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Atypical placental site nodule, placental site trophoblastic tumor, epithelioid trophoblastic tumor

Dr Lok: Welcome to this talk about rare female genital cancers, which is part of the European School of Oncology course. I will be talking about atypical placental site nodule, placental site trophoblastic tumor, and epithelioid trophoblast tumor. Some questions might immediately pop into your mind, like what is the incidence of APSN, PSTT and ETT? And are these rare diseases, and what are the challenges for treating these diseases? And can we use the FIGO scoring like we do for choriocarcinoma and other trophoblastic diseases? And how can we distinguish PSTT and ETT? And as this concerns very young women, can fertility be preserved? The WHO definition of a rare disease is less than one patient from 2000 that is affected with that specific disease. This is a different definition from the European Reference Network that considers a disease rare if less than six patients from a hundred thousand are affected, and this leads to many questions and challenges, both for doctors and for patients. In this table, you see the incidences of the different trophoblastic diseases, and you can immediately see that the diseases in the yellow box are extremely rare. All trophoblastic diseases fulfill the criteria for rare disease, but certainly the placental site trophoblastic tumor, the epithelioid trophoblastic tumor, the exaggerated placental site reaction, and the placental site nodule. Challenges of rare gynecological cancers for healthcare professionals are listed in this table. Of course, there's a small number of patients that are scattered across the country. Often there's only fragmented knowledge. There's limited validated diagnostics and treatments, also, leading to limited expertise and expert centers. There are no evidence-based protocols. They are all consensus-based, because there's no possibility to perform large clinical trials, and it's very difficult to obtain funding from funding agencies, because it's that rare. But also, for patients, there are several problems that they may encounter. There's more uncertainty on treatments, because we lack those large clinical trials. There is often less patient information available. Often, they receive standard leaflets, and not specific for their disease. They have a chance to meet a physician that has never seen this specific cancer before, and they may even receive different advisors in different hospitals, and it's, they have a smaller chance to get into contact with a fellow sufferer. So, in this talk, we will discuss the etiology of APSN, PSTT, and ETT, discuss the diagnosis, then, which stating you have to use to define your treatments, and what kind of guidelines do we have at this moment, and is it possible to offer these patients fertility-sparing surgery. You can consider the trophoblast a tree. The trunk is the intermediate trophoblast, and the leaves are syncytiotrophoblast, and the cytotrophoblast, and

from this latter, the hydatidiform mole and choriocarcinoma develop. The trunk is actually the intermediate trophoblast, but it has two sites. The implantation site, where the exaggerated placental site can develop, but also, the malignant placental site trophoblastic tumor. The villous intermediate trophoblast, which is often situated much closer to the surface in the lower uterine segment, is the origin of the placental site nodule, of the atypical placental site nodule, and of the ETT. Here you see this again in a difference schematic picture. So, the complete and partial hydatidiform mole develops from the syncytiotrophoblast, and the syncytiotrophoblast of choriocarcinoma that develops also from the hydatidiform trophoblast. The placenta site nodule and ETT develop from the villous intermediate trophoblast, and the EPS and PSTT develop from implantation site intermediate trophoblast. You have to know a little bit about PSN before you, we can explain what APSN is. A PSN looks like very small nodules, which are well-circumscribed, and are present in the myometrium. There is central hyalinization, and they're often incidental findings at hysterectomy or in biopsies. They often are present in the lower uterine segment, and in the cervix, but there are rare cases where they are found in the fallopian tube, in the broad ligament, or in the ovary. In very rare cases, they have an atypical appearance, and these appearances have features that are intermediate between the typical PSN and placental site trophoblastic tumor, or ETT. They are usually larger in size compared to the typical PSN. They have an increased cellularity, with more cohesive nests and cords of cells, and mild cytologic and/or nuclear atypia, and there is much more mitosis and necrosis, and if you would do immunohistochemistry, you will find a raised proliferation index. However, this judgment is very subjective, and many pathologists have not encountered any APSN in their working life before. It has not been included yet in the WHO classification, but might be in the near future. The histology of PSCT and ETT can be seen in these figures, in a PSTT, the tumor breaks the myometrium, which is very different from an ETT, where pale cytoplasm and nuclear atypia and necrosis is much more pronounced, but it can be very difficult to differentiate ETT from a cervical carcinoma, especially if the ETT develops in the lower uterine segment, or even the cervix itself, then you need additional testing with immunohistochemistry. This is a very nice figure from the Blaustein Pathology Book, and you can see that with inhibin alpha cytokeratin 18, you can make a difference between trophoblastic lesion and non-trophoblastic lesion. In a second step, human placental lactogen and CD146 can help you to differentiate the site, the implantation site of the more chorionic type intermediate trophoblast, and finally, Ki-67 can help you to say something about proliferation rates. With low proliferation, you have either an exaggerated placental site reaction or placental site nodule, and with higher proliferation rates, you have to consider placental site trophoblastic tumors, or ETTs. Stage is very important for prognosis of PSTT and ETT. This is the FIGO stage in which in the stage 1, the disease is confined to the uterus. In a stage 2, the GTN extends outside the uterus, but it's limited to the genital structures like adnexa, vagina, and broad ligament. In a stage 3, GTN has spread to the lungs, with or without the genital tract involvement, and in the stage 4, all the other metastases are included. For PSTT and ETT, we do not use the FIGO scoring system, as this is not a very good predictor of treatment response, like it is in choriocarcinoma and other gestational trophoblastic neoplasias. It's just not suitable, and you should use the staging, and not the scoring system. The clinical features of the typical placental site nodules are listed here, but a lot of the features are not well-known yet. The largest case series is reported by Baljeet Kaur from Charing Cross Hospital, and she describes 21 cases in young women with a mean age of 35-years that often presented with vaginal blood loss without raised serum hCG. If you consider APSN, but hCG is increased, you have to be aware that transformation to PSTT or ETT might have taken place, and patients can also present with recurrent pregnancy loss often, or an abnormal cervical smear. Most of the APSN behave in fairly benign manner, but some of them are associated with malignant ETT. In three of these 21 described cases, there was either already an ETT or PSTT present, or it developed within 16 months after the diagnosis of APSN. So, the clinical significance remains uncertain, and the differentiation with PSTT or ETT can be very difficult, and expert pathology review is often necessary. Although, it's still very rare, there are many more cases of PSTT described in literature. Clinical presentation is also with irregular vaginal blood loss, sometimes, the other side of the spectrum, amenorrhoea. There can be a persistent increased hCG, but the failure of the hCG is often quite low, much lower than in cases of choriocarcinoma. 70% of the patients present at an early stage with a disease confined to the uterus. If there

are metastases, they are often present in the lungs. The clinical features of ETT are listed here. It's rarer than PSTT. Around a hundred cases are reported. Again, irregular vaginal blood loss might be the first clue. Localization is often in the uterus, but very often in the cervix, or in the lower uterine segment, but luckily, mostly, women present at an early stage. Treatment of these tumors is either surgery or chemotherapy. Surgery is definitely the cornerstone, but in higher stages you might need chemotherapy. What is very important to know besides stage is the interval from the last pregnancy. In 2009, Schmid reported that in 62 cases with PSTT, the prognosis was fairly unfavorable if women were diagnosed more than 48 months after the end of the last pregnancy, and you can see this very well in this graph. So, prognosis was almost perfect before 48 months, but a drastic decline in survival happened if they presented after 48 months. The same has been investigated in ETT by Frijstein et al. in 2019, and the same conclusion could be drawn from these data that prognosis is worse after 48 months. The optimal cutoff was 38 months, but then, the false positive rate was higher, leading to more over-treatment. That's why we still use 48 months as a difference for treatments. So, interval is a very good predictor of poor prognosis of both PSTT and ETT, but that doesn't immediately prove that you should treat it differently, but Fieke Froeling showed in very nice study in 125 patients that if you give chemotherapy, the overall survival improves. He compared two cohorts, one historical cohort from 1976 until 2006, when this interval was not known, and patients were not treated differently, and a cohort more recent from 2007 until 2014, after we knew that interval of 48 months was important, and these women received chemotherapy, including women in stage 1, and you can see the difference in survival. So, if you have a woman with an interval of more than 48-months, you definitely have to consider chemotherapy. What is difficult in rare cancers is that we do not have evidence-based guidelines, so, you need to rely on consensus-based guidelines. This is what we tried to do with the European Organization for the Treatment of Trophoblastic Disease. Based on the literature and local guidelines of 17 different countries in Europe, we drafted proposals for treatment of all the different trophoblastic diseases, including PSTT and ETT. We did not do it yet for APSN, but it will follow in the future. During seven consensus meetings, these proposals were discussed, and the drafts were adjusted, reviewed again, until everybody approved. In this way, a set of minimal requirements was composed, and also a set of best practices, which we were aware that this was not possible to do in all countries, but if you had the opportunity, then, it might improve the care of these patients. These guidelines were published in the European Journal of Cancer in 2020, and you can see how many colleagues have worked on this, and without them, it wouldn't have been possible to compose these guidelines. Here you see the guideline, the flow chart for diagnosing PSTT and ETT. So, the minimal requirement, if you suspect a PSTT or ETT, then you should take a biopsy for histology. If it's confirmed, PSTT or ETT, you should perform a contrast MRI of the brain and the pelvis, and a CT of chest and abdomen. Then, you can determine the stage, and your patients should receive risk-adapted therapy, preferably in a GTD center. A best practice, we think, is if you, very early in the diagnostic path, you already contact the GTD center, what you need to do, and which steps you have to take. It is very wise to have the pathology reviewed by an expert from the GTD center, and as soon as the diagnosis is confirmed, this patient should be registered in the International Database for High-Risk TTN, including ETT and PSTT, and this database is located in Sheffield Hospital in the United Kingdom. So, the treatment of PSTT and ETT is summarized in this slide. If it's a stage 1, based on your radiological findings, and the pregnancy was less than 48 months ago, the hysterectomy and then, surveillance is enough. But if the incidence of pregnancy was more than 48 months ago, besides the hysterectomy, you have to consider platinum-based chemotherapy, and again, after that surveillance. In some countries, they consider high-dose chemotherapy also, an option, and in this day and age where immunotherapy becomes more prominent, we might give pembrolizumab or anything in the future to these high-risk patients, but that's not standard treatment yet. In a stage 2 or 3, you still have to perform hysterectomy, you also have to give the platinum-based combination chemotherapy, and if you have any residual disease after treatment, it's wise to surgically remove this, and then, your patients can go into surveillance again. Also, in this stage, 48 months is an extra risk factor, so, you should do the same as before 48 months, but again, in some countries, high-dose chemotherapy, or other experimental chemotherapy will be considered. In a stage 4, surgery and chemotherapy are the cornerstones before and

after 48 months, and hopefully, for these women with a quite poor prognosis, we can have immunotherapy resolving all residual disease. What's very important if you do the surgery is that you obtain free surgical margins, and sometimes, it's therefore necessary to perform not a hysterectomy, but a radical hysterectomy, as I told you that ETT is often located in the lower uterine segment or in the cervix, so, you should perform a procedure like you are operating cervical cancer, because growth into the parametria has been described, and I think not free surgical margins should be presented. It's very difficult to go back to repeated surgery, and remove remaining parametrium. Sometimes a laparoscopic approach can be chosen. If the lymph nodes are enlarged, you should remove them, but the stem lymphadenectomy is not necessary. There's no evidence that this will improve the survival of your patients, and genetics might help you to differentiate between, for example, ETT and cervical cancer, but also to know from which prior pregnancy the tumor developed, and that can help you with the difference of 48 months, or after 48 months. The order of treatment can be different in higher stage. For example, in stage 4, you can start with the chemotherapy, and do your hysterectomy, and the removal of residual disease after you have completed chemotherapy treatment. In very selected cases, fertility-sparing surgery can be offered, but you have to be very careful with it, because in this table you see that it's not often performed, and that we do not exactly know the outcome. Of course, you should not offer this to women with higher stage disease, but in women with disease confined to the uterus, it's sometimes possible to remove the tumor with a hysteroscopy. Often, the margins are not free, and still a hysterectomy has to be performed. If you summarize all the case reports, you can only find 16 live births after fertility-sparing surgery for especially PSTT, and very seldom for ETT. There is no consensus yet about the best schedule for follow-up. If the hCG is increased before your treatment, you can use this as a marker, and you should continue monitoring it six weeks after normalization, and then monthly during at least 12 months. Imaging is not standard, but should be done upon indication, and according to the GTD center, and the total follow-up should be 10 years, certainly, for the highest stages, because they can recur after many years. Here you see the three tumors listed to enable you to compare the three different forms of TTN. So, APSN affect, it comes from the intermediate trophoblast, can develop into PSTT or ETT, or be present at the same time, and this occurs in 10 to 15% of cases as far as we know at this moment. hCG is not elevated if it is considered PSTT or ETT. Objective criteria for diagnosis are still lacking. Fertility-sparing treatment is often possible, but we will still advise a hysterectomy after fulfilling childbirth, and you have to be careful, and do very close follow-up. There's no consensus yet on an exact scheme for follow-up. PSTT also comes from the intermediate trophoblast with an incidence of 0.1 per thousand pregnancies. A very important prognostic factor is the interval from the end of the last pregnancy of more than 48 months. Surgery is the cornerstone of treatment. Fertility-sparing surgery is possible in highly selected cases. Registration occurs in a worldwide database. hCGs are often low or undetectable, and women often present in stage 1. In ETT, again, from intermediate trophoblast with an even lower incidence than PSTT prognostic factor, also, a stage and interval more than 48 months. Again, registration in the worldwide database. Differentiation with cervical cancer can be difficult, because it's often situated in the lower part of the uterus. Fertility-sparing surgery is not advised. Recurrence of ETT is seldomly curable, hCGs are low, are undetectable, and often, first presentation in stage 1. So, my take-home messages are APSN, PSTT, and ETT are very rare, and the diagnosis can be complicated, so, discuss it with your experts within GTD, and with the GTD centers. You can always reach out to the European Organization for the Treatment of Trophoblastic Disease, and they can help you in treating your patients. Treatment in a GTD center should be considered if there's a GTD center in country. EOTTD guidelines can help you with diagnosis, and with management, and we would love everybody to register their patients with the international database so, we can learn much more about these very rare tumors. Thank you very much for your attention. I know you are not able to ask me questions at this moment, but if you have questions, don't hesitate to mail me. You can see my email address here, and I'm very happy to answer them. Thank you.