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Sex cord stromal tumours:

- Granulosa cell tumours: juvenile versus adult

- Sertoli-Leydig cell tumours

Prof Ray-Coquard: Hello everybody, my name is Isabelle Ray-Coquard, medical oncologist in the Centre Berard, in Léon, France and today I would like to work and to present a tool dedicated to the sex cord tumour, but more particularly granulosa cell tumour. I would like to make a difference between Juvenile and Adult in Sertoli-Leydig cell tumour. My disclosure, so if we go back to the epidemiology, we know that sex cord tumour representing between five to ten percent of all malignant tumour. In term of the most important challenge for this disease, is clearly to identify the patient, to be sure about the prognostic, what is the best standard of care for them and how to optimize routine management and **innovative** strategy and at the end, how to develop international collaboration. In term of epidemiology, as I mentioned before, it is one to three percent of all ovarian tumour, including malignant and non-malignant. In general, we are speaking about patient, in peri and early post-menopausal statues, but we have some pre-pubertal cases. We have to remember that for suspect gonadoblastoma we have to look to the preoperative karyotype, about the risk of dysgenetic gonads. And at the end, the staging program is based on the FIGO stages. In terms of histology, the recent classification has identified pure sex cord tumour, where we have the adult granulosa cell tumour and the juvenile granulosa. We have the mixed sex tumours stromal, including all the Sertoli Leydig and the different subgroup and the pure stromal, where we have the fibrosarcoma and the steroid cell. In term of incidence, our recent publication in the annals of oncology, has report, finally, that there is some difference in term of incidence. With frequently more adult granulosa and Sertoli, compared to the other. But as you can see, the median age is completely different. When we speak about juvenile granulosa, we speak about adolescent and young adult, but it is not the case for all the other. In term of characteristic, clinical characteristic, and prognostic state, when we look at the granulosa cell tumour, we have the adult subtype and the juvenile. The sign includes the symptom of excess estrogen, in fifty percent of the patient. We also have endometrial hyperplasia, specifically in the adult granulosa, but we can be able to see some virilization symptoms and more specifically in the juvenile subgroup. The tumour marker includes inhibin B, Anti-Mullerian hormone and CA-125. And in term of prognostic factor, stage, age, tumour rupture, complete staging and FOXL2 mutation or [Audio Not Clear] 1 can be mentioned. For Sertoli Leydig tumour is, in general, look, in the second and third decade. Seventy five percent of the patient have less than forty years old. And forty percent of these patients have virilization. We also have the FIGO stage, but also the differentiation, the mesenchymal, retiform m elements and DICER-1 mutation as prognostic factor. For sex cord tumour with annular tubule,

we have those sporadic and those associated with Peutz Jegher. In general, they are benign, for those sporadic we have to say that the stage is the most important prognostic factor. Sertoli cell tumour in general are benign tumour. And in this case, we see also some symptom of excess of estrogen but also virilization. And for fibrosarcoma, we have some cases in post-menopausal woman. Is a very rare disease. I have to say that I never seen a fibrosarcoma in my professional life. And we also have some data to consider that perhaps DICER-1 mutation, can be a prognostic factor. In term of diagnosis, is always the same. We speak about pelvic pain, hormonal disorder. Imagery includes CT-scan and MRI. We speak always about the biology before, and we also have to consider a systematic second opinion for the histology. Why? Because for example, in our national network, we have seen that finally, when we systematically organize a second opinion, between the initial diagnosis and the expert, we see some discrepancy between twenty percent for minor discrepancy, but that can move to nine percent for patient where we have an impact on the management of the patient. What about also the molecular diagnosis? We have seen how FOXL-2 mutation and DICER-1 can be interesting and more specifically FOXL-2 for Adult Granulosa cell tumour. where we have seen that could be interesting to increase our capability to give the good histological diagnoses. But we also seen that, in the GNCI publication, the granulosa cell tumour without FOXL-2 mutation, can have a worst prognostic compared to the other. And we also are speaking about, more recently FOXL-2 mutated ctDNA. We have publication report, a correlation between FOXL-2 mutated, blood sample detect, for patient with Adult Granulosa cell tumour. And this can be helpful for the future, perhaps for the diagnosis, but more specifically for surveillance. And response to treatment. In term of difference between adult and juvenile granulosa cell tumour. It is two finally two different diseases. It's not the same age. There is some difference, also in term of stage, in term of morphological aspect. We don't have FOXL-2 mutation, in the juvenile granulosa cell tumour. We don't have DICER-1 mutation in adult. We can have in juvenile granulosa and the recurrence can be very long for adult granulosa cell tumour, then for juvenile, in general is very early since the beginning. And also, in term of morphological aspect, as you can see, provide by Mojgan Devouassoux, it's really two different diseases finally. In term of clinical prognostic factor is the same. We don't have the same prognostic factor for adult granulosa cell tumour, we have FIGO stage, age, intra peritoneal rupture and quality of the surgical staging. For juvenile granulosa cell tumour, stage is the major prognostic factor. Perhaps the tandem duplication of AKT-1, could be this was reported in a publication five years ago and need to be confirmed. For Sertoli Leydig stromal tumour, prognostic factor, include also the FIGO stage, but also the grade and the presence of mesenchymal heterologous elements or retiform component in the literature. We also see some data about the DICER-1 mutation, in the younger population, but we have some publication reporting that could be a prognostic factor in this population. We also look at the pathological evaluation and SIOPe and ESGO have report a publication mentioning that also in the young adult, we need to be careful about, this quality of the analysis and also about the DICER-1 abnormality. And effectively in this context, we have to be careful about any DICER-1 syndrome. DICER is a endoribonuclease RNase family, essential to process microRNAs. And mutation in DICER-1 can be consistently present in a Sertoli Leydig cell tumour. So, the DICER-1 mutation observed at somatic level can be Germline. And so, germline DICER mutation need to be explored, specifically for younger patient, where they can be having an impact on the patient, but also on the family. In term of surgery, the cornerstone of the treatment, for a sex core tumour, including surgical staging, but also radical hysterectomy or fertility sparing surgery. The is frequent question in our national multidisciplinary tumour board, including the role of fertility sparing surgery, the role of hysterectomy and restaging, lymphadenotomy, and laparoscopy versus laparotomy. If we move in the literature, we have now the retrospective data from Van Meurs, we have report for one thousand patients, with adult granulosa cell tumour, that conservative surgery can be completely feasible for stage one, as finally we don't see so much frequent endometrial carcinoma in this disease. And so, we don't need to systematically use hysterectomy. However, evaluation of the endometrium, need to be done to be sure, there is no endometrial abnormality. It is the same for the recent publication, integrating fertility sparing surgery, for early stage. For patient in post-menopausal status. We can consider a total surgery in this context. The laparoscopy versus laparotomy surgery, was analysed by the MITO-9 study, and in this publication, we don't see any difference to use one

or the other. And so currently we considered that both can be proposed for the patient with stage one. In term of lymphadenectomy. We did not mention any benefit to use systematic lymphadenectomy, in early-stage malignant ovarian sex cord tumour. The [Audio Not Clear] database recently confirmed the data, where we have seen that finally, there is very few lymph node involvement in this disease, and there is no data to consider that the surgery of the lymph node impact on the overall survival. Again, what about the restaging? There is some data in the literature to consider that that can be an impact on the PFS, but in the overall survival. And recently, my group have published, retrospective data from the network, including more than five hundred patients. Where we have seen that, the peritoneal staging, proposed in the guidelines, increase our capability, to be conform to the guidelines, but also increase our overall survival, in this retrospective analysis, compared to the patient, who did not have peritoneal staging or endometrial evaluation, for example. What about adjuvant treatment in stage IA? We don't see any benefit to use adjuvant chemotherapy, in stage IA granulosa cell tumour. We only reserve adjuvant chemotherapy for Sertoli Leydig with poorly differentiated, or heterologous element. And there is no place for radiotherapy or hormonal treatment. For stage IC the retrospective data report that there is more relapsed in stage IC than in stage IA. However, when we look at the place of the adjuvant chemotherapy, specifically in the adult granulosa cell tumour, we don't see an advantage to add adjuvant chemotherapy in this staging. For more advanced disease, the risk of relapse is a little bit more important, and we know that chemotherapy, could be efficient in this disease. In this case, we use the BEP regimen, or the carboplatin-paclitaxel regimen six cycle. The data is coming from Jubilee Brown, report that carboplatin paclitaxel give some excellent results compared to the BEP publication. However, the recent GOG0264 randomized phase two trial exploring BEP versus carboplatin paclitaxel, failed to report the benefit using carboplatin paclitaxel. Also, the trial closed for futility, before the end of the recruitment. We don't see a benefit using carboplatin paclitaxel, compared to BEP. Also, the safety profile, is in favour to carboplatin paclitaxel. And so, in general, after fifty years old, we use carboplatin paclitaxel more than BEP In term of guidelines, the recent ESMO guidelines have introduced the active surveillance also for stage one C disease, and we can see their adjuvant chemotherapy, only for more advanced disease. The surveillance will need to include long surveillance as we have seen a relapse after ten years old. In term initial management, the key message is, systematic histological review, FOXL2 and DICER1 mutation research, to offer to improve diagnosis. Surgical managing can be conservative for early stage. Complete surgical staging need to be offered to increase overall survival. There is no benefit of adjuvant chemotherapy in stage one. For advanced disease, the level of evidence is low and the management by expert centre is greatly supported. In advanced disease and in relapse, we know that the risk of relapse is close to, thirty six percent and can be between two to twenty-three years. So, we have to look at the patient for very long time. And in this case, we have several options that we will discuss right now. There is a rational for surgery, because we speak about indolent disease. And we know that the relapse in general is in the pelvic, or abdominal or retroperitoneal. The surgery is completely manageable with a few mortalities and morbidity acceptable, but we have to remember in this case that, if we would like to propose surgery for this patient, the surgery need to be complete. And there is no benefit to use HIPEC in this disease. There is also a publication to confirm that, the MITO-9 retrospective data report, how the quality of surgery needs to be good. If we would like to increase the overall survival of the patient, using surgery in this setting. There is also a rationale for chemotherapy because there is some data to report response rate using chemotherapy in this disease, between 20 to 80 % depends of the data. This could be proposed when there is no alternative and more specifically when there is no place for surgery. However, the question currently is, after complete resection, do we have evidence to use, so do adjuvant chemotherapy, right now, we don't have data to consider that after complete surgery, also in relapse, there is benefit to add chemotherapy yes or not. In term of hormonal treatment, we have some rationale to consider hormonal therapy, because the tumour commonly express ER and PR. It is an optimal treatment for indolent disease. We have retrospective data reporting case report, with a good response rate using antioestrogen therapy. And in term of biology, we know that there is a deregulation of the TGF beta pathway. We have reduction in apoptosis, we've had expression of the TNF receptor one. We also be able to induce general apoptosis and there is a link between

FOXL2 mutation and CYP19, that it is the aromatase gene involved in the activity of an aromatase inhibitor. We also as mentioned before, have some data to report efficacy, of different hormonal therapy in the literature. And in this context, we can see there that aromatase inhibitor should be the best. However, we have some retrospective data from the PARAGON study, two years ago, and now published in the GINECO paper, where finally the use of anastrozole in this setting, did not report so much efficacy. Only one patient with partial response and the median PFS of eight months is not so good, considering the very indolent disease, about adult granulosa cell tumour. We consider that perhaps the TGF B pathway, should be interesting to explore in such context because of the link between FOXL2 mutation, SMAD three pathway and the TGF and active in a pathway. We need to wait for more clinical data, before to move in this direction. About angiogenesis, we have preclinical data to consider that VEGF could be interesting in the setting, and we have a phase two trial report, by the GOG using bevacizumab. With response rate of 17%, a median PFS of nine months, that can be good. And in this context, we have developed the ALIENOR phase, a randomized trial exploring the combination of paclitaxel plus Bev versus paclitaxel alone for patient who already receive platinum-based chemotherapy. This randomized trial is now published in the JAMA oncology. And we have seen some interesting data. First, the median delay between the initial diagnosis and the first relapse is ten years is not months. We see that the vast majority of the patient, are adult granulosa cell tumour. There is few other histology in the relapse setting. And finally, the vast majority of the patient, were diagnosed with early stage. In term of treatment, in the ALIENOR data, we have seen that the patient receives at least two surgeries before, to be considered not able to receive surgery, but you can see that some of them receive until six or eight surgeries before to be candidate for chemotherapy. All the patients for sure in the trial, receive platinum-based chemotherapy before and in general they receive at least two lines of platinum-based chemotherapy before to be considered platinum resistant in this trial. If we look at a very good response rate, using the combination, with forty four percent compared to only twenty five percent using paclitaxel alone. Unfortunately, we don't see any benefit in term of median PFS in this population of patients. And it is the same for the overall survivor. In term of a new drug, there is some data to consider that antibody targeting the Mullerian receptor hormone. We have seen some data in the phase one, we hope that phase two will be available in the future. There is the ACSé program using pembrolizumab in sex cord tumour with ten patients, including the results will be available next year. There is some case report, reporting efficacy of aromatase inhibitor + mTOR inhibitor, and we are waiting for more data in the future. HDAC inhibitors, CDK4, CDK6 inhibitor are also something interesting in this context of tumour with hormonal pathway, but there is also a Src inhibitor, weekly paclitaxel and mTOR inhibitor in cell models that could be interesting for the future. In term of HDAC inhibitor, we have report several years ago, good results specifically, for Sertoli Leydig tumour. With a very long efficacy using a HDAC inhibitor, but unfortunately there is no more data, until now using this drug. So, the summary for the relapse, is that we need to consider surgery, whenever we can do it, hormonal treatment could be interesting for selected case, probably adult granulosa cell tumour but we don't know exactly when. When chemotherapy with platinum base is not an option, the weekly paclitaxel is a standard of care and clinical trial & translational research need to be developed for these patients. The unmet need is really to define the risk factor, to know if there is any place for adjuvant chemotherapy for the future. And also, we need to develop, a new organization for the future. It is what I mentioned at the beginning of my talk. New organization at the national level, new organization, and new collaboration at the international level. I just want to focus on the French organization because we have proved by the past, how we are able to change this, looking to what we have organized, including several national and regional experts centre, able to delineate multidisciplinary tumour board for all the patients in everywhere in France. We also develop a systematic to double reading molecular analysis for all the patient and for sure education and clinical research. We have seen with the Alienor trial that, the national organization plus the international collaboration are able to move in a randomized phase two trial, in a very rare disease. So, it's important for us to remember, we need also to develop and to update the GCIG guideline. It is what we have done recently between the GCIG and the ESGO. And the new guidelines is already available on the ESGO, smartphone application. And finally, the last but not least, we need to develop more clinical trial dedicated to molecular

screening and the PETAL program where we look at molecular abnormality and then we move to clinical trial is really the future. Also, for this disease. The take home message for sex core tumour, is to consider that they are not so rare. We have to be careful about radical surgery and adjuvant treatment. We are not sure we need it. We need to have expert pathology, multidisciplinary board and dedicated rare cancer network to be sure at the end that we will be able to increase our capability to cure the patient. Thank you very much for your attention.