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Renal tumours of childhood (held in collaboration with SIOPe)

Dr Graf: MY Name is Norbert Graf, and I will speak to you today about renal tumours of childhood. As you may know, renal tumours in childhood are not only one kind of tumour, most important is Wilm's tumour or nephroblastoma, which is accounting for nearly 90% of all kidney tumours. There are localized nephroblastomas, there are nephroblastomas with metastatic disease and there are around 10% of Wilm's tumours or nephroblastoma that are occurring in both kidneys. As you can see, here is also other parts of kidney tumours that are rarely seen as the congenital mesoblast nephroma, the clear cell sarcoma of the kidney, the malignant rhabdoid of the kidney and others, and even there are some benign tumours. You may all know that the outcome of nephroblastoma is very good. Over the last decades the survival rate of these patients did really grow up and now we have around 90% of survival. But what you also can see that over the last nearly 20 years there's no progress and not higher survival rates. We do know to better stratify patients according to their own risk, but there's still a threshold not to really solve the problem for every child. Worldwide there are only two big study groups for kidney tumours around the world. This is one hand the COG, which is the Children Oncology Group in Northern America, and this is the SIOP, mainly in Europe, but in the meantime spread around the world. And as you can see here in this slide, there are two different philosophies between COG and SIOP. In COG treatment starts always at primary surgery, whereas in SIOP we start at preoperative chemotherapy. In both groups we have risk factors and mainly some risk factors are the same, like stage, histology, tumour volume, response to treatment and the age. But response to treatment is looked for in all kidney tumours, whereas this is only the case in stage 4 nephroblastoma in the COG. And in comparison, COG is using molecular markers in their last studies, and they start to use new molecular markers for stratification. I will come back to that later on. Whereas we in SIOP have chosen blastemal subtype as a risk factor. But looking into that you see that the loss of heterozygosity one P and 16 Q or the blastemal subtype are not more than 5 to 10% of all the cases of nephroblastoma showing a poor event-free survival, and poor overall survival for these patients. So in both study groups there's a need for additional molecular markers for better stratification. Why did we choose preoperative chemotherapy in SIOP? You can see that easily in this CT scan of a child with a nephroblastoma at a time of diagnosis, and the same child after four weeks of vincristine and actinomycin D. You see how much the tumour did shrink in this kidney. And that would make it also possible to do kidney or nephron sparing surgery. In SIOP 9, one of our clinical prospective trials, we had a randomized question to ask in four weeks of preoperative chemotherapy or eight weeks after preoperative chemotherapy are better. As you can see, tumour volume is decreasing constantly, but the stage distribution after surgery is completely the same. So after that trial, the four weeks of preoperative chemotherapy became the golden standard of treating children with nephroblastoma. The other reason for having preoperative chemotherapy is the down-staging of the tumour. You see here the different SIOP trials up to SIOP 9, and you see how they were distributed in their stages after primary surgery, after preoperative irradiation, or after preoperative irradiation and chemotherapy, and only chemotherapy.

And you can see the number of stage three is going down, whereas the number of local stage one is going up. And you also can see that a number or the percentage of tumour ruptures from around 20% after primary surgery is going down to less than five percent. So there are many good reasons to do preoperative chemotherapy. And you can see that in stage four as well. Here a patient with metastatic disease to the lung and then you see after preoperative chemotherapy how these lung metastasis are vanished and around 50% of all patients with lung metastasis will have a complete remission after preoperative chemotherapy.

Dr Friesenbichler: Dr. Graf, may I interrupt you for a moment on the subject of pulmonary metastasis?

Dr Graf: Yes.

Dr Friesenbichler: According to the last SIOP protocol pulmonary metastasis were only diagnosed if nodules were visible on the X-ray and a CT was not recommended. The Umbrella Protocol instead recommends a chest CT in all patients and even nodules as small as three millimetres are considered metastatic. So do you expect that more patients will require lung irradiation as a result of this change?

Dr Graf: No, we'll not think so. We have looked in SIOP 2001, and this is a paper published. [Audio Not Clear] Where we have divided the patients in three groups. One group were patients we had as a diagnostic procedure only in X-ray of the lungs, others had also CT scan. And then patients could be divided in those having others metastatic disease in the X-ray, others who had metastatic disease in the CT scan and the X-ray, and others having only in the CT scan metastatic disease. And then we compared the outcome of these patients, and we did see that the best were those who had no metastatic disease in the CT scan. The worst were those with others metastatic disease in the X-ray shown. And in between were those who have only CT nodules or only metastatic disease seen in the CT scan. And these patients were treated according to localized disease. And that means to have a better diagnosis at the beginning of the staging. These patients would benefit from a more intensive treatment. And as we have only in those patients who will not go into complete remission to the lungs and who will not have the possibility to take these nodules out, they will receive radiotherapy to the lungs or if they have high risk histology.

Dr Friesenbichler: Okay, thanks a lot.

Dr Graf: Thanks, so as you can see here, we have started, the same is true for the COG, at the beginning of the 70s in the 19th century with prospective randomized multi-centres trials. What you can easily see is that a number of patients is increasing over time in the different trials, but what you can also see is the first trial did take only three years, the next two years, and the following is always starting the same year when the last trial stopped. And as you can see, this is now completely different. We do need more time between the trials. And you see here this trial stopped in 2015 and we started the umbrella in some countries last year. What we see here, the number is increasing, the number of participating countries is increasing, and the number of hospitals is increasing. This might be very complicated to look at that, but it shows you how the stratification for nephroblastoma is done, in SIOP we have those with localized disease, those with metastatic disease, and those with stage five disease. And as you can see, they all receive preoperative chemotherapy and after surgery, sorry, after surgery they will be stratified according to the histology in low, intermediate and high risk and according to their staging. And that means that part of these patients will receive no treatment after surgery, these are patients with stage one and low risk, these are mainly completely necrotic patients, these are around five percent of patients, and it goes up to a high risk protocol in stage three and high risk tumours with four drugs plus irradiation. I will not go into detail in the other parts because of time constraints. There was a question in SIOPe 2001, that was a question about randomization in stage two and three after preoperative chemotherapy in intermediate risk groups. The question if we can avoid anthracyclines. And as you can see here looking into the overall survival, there you see a super imposable life table with overall survival of more than 90% for stage two and three independent of anthracyclines or not. Also for the event-free survival, there's no significant difference, and the question was to spare some relapses that can be cured in a second attempt, we would need to treat 21 patients with anthracyclines to spare one

relapse. So we decided not to give further anthracyclines in the intermediate risk patients with stage two and three. Nevertheless, the outcome of patients according to the histology and the staging is in these patients excellent, and in these patients with stage three and stage four, especially in stage four and high risk tumours there's only a survival of two years of 36%, which is very low for children with nephroblastoma.

Dr Friesenbichler: Two questions in the chat. So the first is when do you do a biopsy preoperatively?

Dr Graf: Yes, this is a good question. We had a discussion in our group about that. And we did see when we looked into the different histologies that with the beginning or between 7 and 10 years of age the number of renal cells carcinoma is rising. And there is a question if we would start in this age group with biopsy to confirm this is nephroblastoma or not. As you also know that in patients below the age of six months we always go for primary surgery because the number of congenital mesoblastic nephroma is much higher than from nephroblastoma. So you want to spare chemotherapy for these patients. Beyond the age of 16 to 18 every patient should go for primary surgery.

Dr Friesenbichler: Okay, thank you. And the second question is: does a high dose of chemotherapy play a role in the treatment of high risk Wilm's tumours?

Dr Graf: In the primary part of high risk Wilm's tumour not but in the relapse situation, if we have a relapse then we will also go for high dose chemotherapy with autologous stem cell transplantation, but not in all of the relapses, only in those with high risk relapses.

Dr Friesenbichler: Okay, thanks a lot.

Dr Graf: Thanks, so I will continue. If we go into new trials for nephroblastoma, we can think about future directions. What we all need, and that was shown before, we all need a better risk stratification. We should avoid acute toxicity and late effects, but we also have to look into quality control, we have to look into our IT infrastructure and logistic to change the data. And what is very important is international collaboration. I will go into detail in all of these subjects. So first to response to treatment. One important issue in this aspect is pathology. In pathology we'll get some information about the tumour volume, we get information about staging, histological classification and we need to look into biomaterial, and we hope that biomaterial will give us new risk factors. Looking into the pathology in more detail, pathologists primarily have to look when they go into examining the specimen is the anaplasia yes or no. If they see diffuse anaplasia automatically this tumour is a high-risk tumour with diffuse anaplasia. Is there no anaplasia or only focal anaplasia, the pathologist has to look how much regression is seen. If there's 100% regression, this is a complete necrotic tumour and is a low risk tumour. Is there less than 66% regression? Then you have to look into the vital tumour and check which parts of the vital tumour are there. And if there's more than 66% of, for example, epithelial type or stromal type, then you call it epithelial or stromal type, this intermediate risk or you call it blastemal type high-risk if there's more than 66% blastema in the tumour. If there's more than 66%, but less than 100%, you call this a regressive type. And if there's no part more than 66%, you have a mixed type of nephroblastoma. And so you come up to very complicated histological classification. And what happens during preoperative chemotherapy to histology, and you see here some changes. One change is regarding post chemotherapeutic changes, regression, this can only be seen in patients who receive preoperative chemotherapy. And the other one is the decrease of blastemal cells after preoperative chemotherapy. Normally, one third of all the nephroblastomas are blastemal predominant, after chemotherapy it's around 10%, and these 10% of patients do worse. So these blastemal subtypes are called also high risk and they were treated according to high risk. The next point that will stratify patients in our mind is tumour volume. Here if you look after preoperative chemotherapy into tumour volume you see a difference between those tumours with less than 500 millilitres and those with more than 500 millilitre of tumour volume. This is highly significant in difference. But what is the reason for that? If we look into again what we have defined and found, the blastemal type of tumours that is high risk the question is how really significant is that. I have here two different patients. Both have the same tumour volume. The percentage of necrosis is nearly the same,

but it's different. And the percentage of blastema is 70% or 90%. You see here, because this is a tumour with more than two thirds of necrosis, it is called a regressive type, this one with less than 66% of necrosis, and more than 66% of blastema is called blastemal subtype. If you calculate the absolute volume of the blastema in these two tumours, this is nearly the same. But they are treated completely differently. So this tumour is treated as a high-risk tumour with the blastemal subtype, and this is treated as an intermediate risk tumour. A big difference in treatment. That was the reason why we looked also in the absolute volume of the blastema. And here is localized Wilm's tumour intermediate risk. And in this Martingale plot you see here a threshold, and this threshold is about 20 millilitres where there is an excess of relapses in the retrospective analysis. And if you go for that reason into life table, Kaplan-Meier curves, you see even the regressive type as well as in the mixed type. If you have more than 20 millilitre of blastema, these regressive type tumours do worse than those with less than 20 millilitre. And the same is true for the mixed type, and the same is true for this epithelial or the stromal type. If we go for stage four, as these patients receive six weeks of three tracks and then only four weeks of two tracks, already 10 millilitre of blastema shows through here an increase in relapses. And if you put that into a live curve you see here those patients with less than 10 millilitres in metastatic disease and more than 10 millilitres, you will see a big discrepancy between the outcome of these patients. All this is based on retrospective data, this will check in the now-running umbrella study prospectively, and we do need a pathologist to tell us and help us to define this exact volume of 10 or 20 millilitres. Are there any questions at the moment? If not, I can continue also. And maybe questions come up more. I will go for molecular biology now. There's a lot of known about the biology of Wilm's tumour. But it is very complicated. There are many different somatic mutations that are known in Wilm's tumours, there are also germline mutation, and you can see that there is also correlation between different histological subtypes. For example, WT1 and the stromal subtype. TRIM28 and epithelial subtype, or P53 and anaplasia. And what is looked now into more detail, a chromosomal copy number gains of one Q and it's long shown by the COG mainly that loss of heterozygosity in one P and 16Q have a very important aspect in the outcome. Here the question of also from retrospective data and this was shown here by SIOP, but the same analysis was also done by the COG, both papers were published in 2016 in the same issue showing that in the event-free survival there's indeed a difference in outcome between those with a gain of one Q and those not having this gain of one Q. And there is also an overall survival difference significantly. The question is, is this related to blastemal subtype as well.

Dr Friesenbichler: Norbert, may I interrupt you here?

Dr Graf: Yes.

Dr Friesenbichler: There's one question in the chat. So how do we calculate the volume of blastema if there is a multicentric tumour?

Dr Graf: That's a good question and therefore we do need a pathologist, so this is always somehow, they judge about it. So they see several areas, and the question that is also discussed is that something that has also an effect on outcome, as you have also the question of diffuse and focal anaplasia. Focal anaplasia is not seen as a risk factor, at least in the SIOPe, whereas diffuse anaplasia is high risk tumour. And a question of multifocal blastema is in the moment seen as you will put them all together as part of the blastemal subtype.

Dr Friesenbichler: Okay, thank you. And the second is, are there already results that indicate that one Q gain and blastemal subtype correlate?

Dr Graf: Yes, there are some results that are correlated and we think that there is a connection to it. But therefore I want to show you this picture here or this slide here. If you look into one Q gain, and you would have the same tumour of one patient, sorry, and would take out tumour material for molecular analysis at different areas of the tumour you will see that you will not find in the same patient in all specimens one Q gain. So it might sometimes, if you take only one specimen out of acute tumour that you will miss the one Q gain. And therefore the question is how much of these samples do we need to take out to get information

about the intertumoral heterogenicity and this would have a lot of implications for tumour sampling in the future. The other way around how we can try to overcome this problem might be by looking in liquid biopsies. Here is a picture of liquid biopsies taken from micro RNAs and in each of these pictures you see here this is 1026 micro RNAs in one patient, in another patient, in the next patient. And these expressions of micro RNAs are coloured. And if you compare different patients together you can run another bioinformatic tool about it, a SOM and a second SOM as a self-organizing map. And you can cluster those that look in the same way. Like here, you have here a cluster of patients here and you have a cluster of patients here. If you look here in these patients into the histologies, these patients here, for example, are high risk patient. And if you look into the molecular biology behind you see that these micro RNAs are dealing with a disruption of apoptosis with more proliferation. And if you look into this area of the self-organizing map, then you see these are correlated with patients that are regressive type. And interestingly you find here micro RNAs that are stimulating the immune system. So the question is, can these liquid biopsies help us also to cluster patients, to stratify patients, and this is not a question we try to solve prospectively in the running umbrella study. Again, are there questions?

Dr Friesenbichler: No, for the moment you answered all the questions.

Dr Graf: Okay, perfect, then I will go to the imaging. Imaging is making a lot of progress, and as you can see here, if we are looking into MRIs, we cannot only look into the volume of the nephroblastoma, but if we also use the diffusion weighted imaging, we can also look into the ADC value. And the ADC value always correlates with the subtyping because the more cells you have the less water molecules can flow. And that means a high cellularity will show a low ADC value. And that will tell you if you have a low ADC value, you have lost a lot of cells. And here, for example, you can compare the ADC value and the tumour volume, and you do see not only a shrinking of the tumour, but also a change of the ADC value. The higher the ADC value, the less cellularity it is. And this is in different patients where you can differentiate that, and this is something we want to correlate also to the pathology behind. What is also a very important issue in treating patients with nephroblastoma is minimization of acute toxicity and late effects. SIOP 2001 did show us cardiotoxicity can be answered that we do not need any anthracyclines in intermediate risk stage two and stage three patients. So in intermediate risk patients, and no metastatic disease, no chemotherapy with anthracyclines is given. Neither in stage one, nor stage two, no stage three. Only in high risk or in patients with metastatic disease. And nephrotoxicity, of course, is also something we have to look into that. So the question of late effects in the SIOP shows that there's a low rate of late effects, but we need to say that we have not systematically looked into late effects in the past studies. This will be done in another way in the upcoming umbrella study. Cardiotoxicity remains a problem for those patients with stage four disease that also receive lung irradiation because anthracyclines plus lung irradiation increases the risk of cardiomyopathies. And there's still the questions how far can we further reduce anthracyclines. The minimization of radiotherapy is another important step in optimizing treatment strategies, and the moment the radiotherapists are thinking about new fields how to safely apply radiotherapy to the patients, this will be prospectively measured in several centres, and then it might come up with other areas that needs to be irradiated. The down-staging of preoperative chemotherapy is an important factor for the reduction of late effects in nephroblastoma. This is one reason for the upcoming trial for metastatic disease where we want to show if we would increase the intensity of preoperative chemotherapy with carboplatin if that would reduce the number of blastemal typing in the nephroblastoma and also the volume. This is a question we want to answer in the upcoming randomized trial, as we call it.

Dr Friesenbichler: May I interrupt you again?

Dr Graf: Yes.

Dr Friesenbichler: Because there are two more questions in the chat.

Dr Graf: Yes, of course.

Dr Friesenbichler: The first is, again, concerning one Q gain.

Dr Graf: Yes.

Dr Friesenbichler: So you said one Q gain is related to blastema subtypes, what happens in more faithful re-histology?

Dr Graf: The question can't be answered in the moment quite clearly. Because we do not know because of the intertumoral heterogeneity if there are some patients having one Q gain that was missed. So we do need exactly more data to answer that question.

Dr Friesenbichler: So if faithful re-histology is connected with one Q gain, should these patients get a more intense treatment?

Dr Graf: This is done in the moment in the U.S. in their COG trails. So they have used that in the upcoming COG trials that one Q gain is a risk factor for them.

Dr Friesenbichler: Okay.

Dr Graf: And they have the faithful re-histology, yes.

Dr Friesenbichler: And there's another question, is there a role for dexrazoxane in Wilm's tumour?

Dr Graf: This is also a good question. This was never asked in a trial, in randomization, this is something nobody has looked into that. There's sometimes this question coming up and if you have a patient that wouldn't need a very high dose of anthracyclines, and that might have already had a lung irradiation or needs a lung irradiation where you cannot spare the whole heart out of the radiation field, then I would recommend to give it.

Dr Friesenbichler: Okay, thanks a lot.

Dr Graf: Okay, then we would come to quality control. And quality control is a very important issue. Because we do know that even if we look into Europe, and even if those patients have the same treatment, there is a discrepancy in outcome. And even if we look here into data in Germany where we have here looked into the number of patients treated in the hospital, and how big these hospitals are, we do see there are some hospitals that treat less than one patient a year. These are half of our hospitals in Germany, this is several years ago. Treating only 115 patients, and there are only eight hospitals in Germany treating more than four patients a year with nephroblastoma. Even this is a low number. But they already treat nearly one third of all patients in Germany. And these, more than 100 hospitals are now going down to 40 hospitals. So that this is different, but is that needed? You can see here with a simple analysis looking into the ruptures. And the number of ruptures or the percentage of ruptures in those small hospitals, all ruptures are much higher and significantly higher than in these bigger hospitals. And also these major ruptures. The outcome is the same, but these patients do receive radiotherapy that is not needed for these patients. Therefore quality control and experience is important. Now, you can also ask, oh, maybe the small hospitals treat patients with bigger tumours or with more poor histologies? No, this is not the case, here are the bigger tumours, these hospitals have the smaller tumours. So this is really a question of quality control. And this affects than biology in the moment the outcome of the patients. You can ask also about nephron sparing surgery. Also in unilateral, we do it in bilaterals. And the outcome is the same. This was published already 17 years ago, and in the moment we do discuss for those patients always nephron sparing surgery, in unilateral cases if it is possible we have our surgeons, we have a panel, and with whom we do discuss these cases in a single situation of the patients.

Dr Friesenbichler: May I ask a question with this topic?

Dr Graf: Yes, yes.

Dr Friesenbichler: Because currently we have a child who had a nephron sparing surgery. Unfortunately, the resection margins were not negative. So how would you proceed? Would you recommend a second surgery and have a complete nephrectomy that time?

Dr Graf: This is a good question.

Dr Friesenbichler: It's a unilateral tumour, it's a unilateral tumour.

Dr Graf: It's a unilateral tumour, this is a good question. The problem is, if you have vital tumour at resection area, the child does need radiotherapy. And this is not very nice. Because the radiotherapy will also have an impact of the normal kidney. I would say you need to go and take the kidney out if the tumour is of high risk, if this is an anaplasia, and if this is a blastemal subtype. Because these patients have a higher risk of getting a local relapse as well even after radiotherapy. So this would be one reason to do so. If it is an intermediate risk, and if in the rim of the resection there is regressive tumour or necrotic tumour only, then I would not go to take the kidney out. But this should always—

Dr Friesenbichler: It's intermediate subtype with vital tumour at the pre-section margin.

Dr Graf: With vital tumour. Then I always would go to the family and would discuss also with the parents.

Dr Friesenbichler: Yes, okay.

Dr Graf: ut you can never spare the radiotherapy, this is much more problematic as we had also such a child where somebody did try to do nephron sparing surgery in a child where we would have said, don't try it, and this was a small baby. And now this baby needs indeed radiotherapy to the abdomen. So be careful with the indication of nephron sparing surgery, yes.

Dr Friesenbichler: Okay, thanks a lot. And there's one more question in the chat.

Dr Graf: Yes.

Dr Friesenbichler: Somebody's asking whether stromal type stage four tumours have an indication for lung radiotherapy?

Dr Graf: Most important for the stromal subtype is that you can take out all metastatic disease in the lung. The problem of stromal tumour subtype is that they do not respond quite well to the chemotherapy. So if you have, for example, a bilateral tumour that is not shrinking under preoperative chemotherapy, you always should think about a stromal subtype. And mainly they have the stromal subtype, and mainly they have the double UT one mutation. And that might also be a mutation not only in the tumours, but you will find that, so you should look for the double UT one mutation in bilaterals. And the question is always going to the surgeons in that situation. If you have a stromal subtype and you don't see a response to chemotherapy, please go for take the tumour out and do that also for the metastatic disease. If you achieve a complete remission by surgery, also in the lungs, then no radiotherapy is needed. If you can't achieve that, of course, these patients do need lung irradiation if there's still metastatic disease. And if there's over—

Dr Friesenbichler: Okay, thanks.

Dr Graf: Metastasis, maybe you should also boost them.

Dr Friesenbichler: Okay, thanks a lot. [Audio Not Clear] it popped up another question in the chat.

Dr Graf: Yes, yes.

Dr Friesenbichler: If there's a gap of three months between surgery and the of chemotherapy due to Covid-19, how will you proceed? The initial tumour had capsular invasion, no invasion of veins, no rupture. Focal anaplasia with blastemal components are seen.

Dr Graf: I would not change the treatment at all. I would check if the child is still in a complete remission. This is the first thing I would do because three months of time without chemo is a lot of time. So I would do again a staging for the child. If there's now, for example, metastatic disease, then, of course, change the treatment. If the child is still in complete remission, I would not change the treatment at all. But would continue with the treatment that was given for the staging and the histology.

Dr Friesenbichler: Thanks a lot, Dr. Graf.

Dr Graf: Okay, then we can proceed. Then we have here IT infrastructure and logistics. Which is also important, and I will show you one slide for that. As you can see here, and that dictates how we have to deal with the future. And this is, if you look for treatment patients did receive, then you see that a number of relapses in absolute terms are more in those patients receiving only vincristine and actinomycin D more than in the stage four patients. But you see, you can rescue these patients, but you cannot rescue all the stage four patients. So you see the absolute number of relapses is the highest in the lower risk group patients. Therefore only reducing treatment in this group of patients will not help you, that might cause more relapses. And you will not make a better outcome for all the patients if you would increase treatment for stage four. So therefore we need to go in more details how to deal with that. And if you look for the patients who will not survive, they are of course here in this risk group. Therefore the combination of imaging of molecular biology, pathology and everything is now prospectively analysed in our hospitals in very distinctive ways in a European project to see if we can build up a model that will predict in the individual patient how the patient will respond to preoperative chemotherapy based on all these findings, we will get. And I hope we can deliver in one to two years first results of that. Then international collaboration is important because if you have a high cure rate and you have a rare tumour, and nephroblastoma is a rare tumour, you will get only better outcome if you participate and collaborate. And here you see the participants of our last SIOP-RTSG meeting, and this is coming from more than 35 countries, and more than 157 participants. And all of them, besides North America, are taking part in our upcoming clinical trial umbrella. And this is the new trial we have started last year. And the goal of that trial is to increase survival rates, reduce acute and late toxicity, and, and this is very important, to provide high quality of a standardized diagnosis treatment and follow-up independently of the tumour type, the socio-economic status and a geographic region where the patient is living. And as you can see here, China is participating, we already have enrolled Shanghai, and hospitals from Guangzhou, from Hong Kong that will participate as well as two hospitals from Moscow. So we need to really increase survival rates in all regions in the world. And we have here an integrated research protocol, we are not asking randomized question in the localized one, we ask this in the metastatic ones, as I told before. So we provide standardized guidelines that the treatment will be the same, the diagnostic procedures and hopefully the outcome for all patients in SIOP. But we also need the involvement of parents' groups and long-term survivors to tell us what should be the first issue in looking into research and other topics. So I hope I could show you that we started from staging, histology, up to biomarker and hopefully increase the outcome of patients with nephroblastoma. These are acknowledgements I have to give to several European projects and funding areas for nephroblastoma. And thank you for listening.

Dr Friesenbichler: Thank you for this very interesting presentation. And thanks for the vivid discussion. There are no more questions in the chat.

Dr Graf: Okay, thanks a lot.

Dr Friesenbichler: Thank you.