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Principles of treatment of osteosarcoma

Prof Bielack: Hello, today's lecture is about osteosarcoma but first of all, let me greet all of you and let me tell you that I hope you're safe and your families are too. So, osteosarcoma. When do you have an osteosarcoma? You might have pain in your limb usually around the knee of around one to three months duration, you might have a swelling in your extremity or probably somewhere else. Then you might have immobility of the neighboring joints and sometimes, you will have a pathologic fracture. So, all in all, if you don't have fracture, you're quite healthy, have some pain in your extremity, systemic symptoms are absolutely rare. Now, before we go any further, let me tell you to look at the ESMO guidelines, ESMO-PaedCan-EURACAN Clinical Practice Guidelines for Bone Sarcomas. There it says, all patients with a bone lesion that is likely to be a primary malignant bone tumor, as osteosarcoma, on a radiological basis should be referred to a bone sarcoma center or to an institution belonging to a specialized sarcoma network. Children and adolescents should be referred to centers which in addition provide age-specific expertise. That means, if you're not in the center, if you're not a specialist and then, if you're dealing with a child, if you're not a pediatrician, send your patient to someone else. What is osteosarcoma? Osteosarcoma is a malignant mesenchymal tumor with osteoid, which you can see on the slide, produced by the malignant cells. Every malignant tumor that has osteoid producing malignant cells is an osteosarcoma by definition. Of course, there are several different subtypes which you can see in the WHO classification. You have conventional ones of different types, you have teleangiectatic, small cell, high grade surface. They're all treated the same but then, rarely, usually more older patients, you have some lower or some subtypes of lower malignancy parosteal, periosteal, low-grade, central and what I'm telling you it's not about those subtypes but it's about the highly malignant conventional teleangiectatic, small cell, high-grade surface subtypes. If you have a patient with an osteosarcoma, you might want to take a closer look at him. There is some germline and somatic genetic alterations which might confer a higher-risk. We're not quite sure how many there are, maybe, 10%, 15%, 20% with the new genetic diagnostics. And you want to know that before you start your treatment because some of those symptoms interfere with it. Why am I, as a pediatrician, talking about osteosarcoma? You can see that here, on the blue line, osteosarcoma is a disease of adolescents. The peak is in adolescence and the incidence goes down once you're an adult but as you can see here, on the right, the incidence climbs again when you're very old and that's mainly because of secondary osteosarcomas and of asteosarcomas in association with age's disease. So, in summary, we have an incidence in the population of 2-3 per million per year, we have adolescents mainly affected, for sex, there's a slight male predominance of

maybe 1.4:1 and the site is the metaphyses of the long bones. It's the femur, proximal tibia, proximal humerus, proximal fibula but of course, it may arise anywhere else in the body particularly, in older patients. As you can see here, you see the incidence of osteosarcoma, the strong line, then you can see a very slight line and a slight gray of adolescents and of extremities and you see the trunk, a little bit stronger, the little line on the bottom and you see that they meet and add about 40 years. So, all the patients, the proportion of axial osteosarcoma is much higher. You might want to operate on osteosarcoma and it's in an extremity. You can, if you're not a good surgeon, you can amputate. You will not have cured the patients that's because of metastases. If you look in the beginning you will find metastases in maybe 10%, 15%, nowadays, maybe, even 20% of patients and the most often, as this slide tells you, are located in the lung. Secondly, the bone, and rarely, in other sites. There's a specific finding, which are so-called skip-metastases in the bone, that's second lesions which are not adjacent to the primary tumor but close to the primary tumor. And this picture here, this graph shows you that we do have the stage migration in our registry or study group. We had around 10% of patients with primary metastases around 1980 and now, we have 20% and another 10%, we don't really know because equivocal findings upon imaging and that shows the biology hasn't changed, imaging has changed. So, you cannot compare results which were obtained in studies 30, 40 years ago with those that were obtained recently because you will have another selection of patients. Which questions need to be answered by imaging investigations? It's quite easy. You want to locate your primary tumor extent; you want to see how far the disease has spread in the bone. Osseous extension, you want to see how far it's spread the marrow, intramedullary spread, want to see if it's escaped from the bone so are the soft tissues next to it involved and how are the neighboring structures, usually, the joints affected. And then, you want to see if the patient has primary metastases and that means you need very good imaging of the lungs because osteosarcoma metastasizes to the lungs. You also want to look at the bones, distant bones, other organs, maybe, the lymph nodes, other organs, it really happens, and if it happens, it's usually a widespread disease, you can't do anything anyhow. So, you should really focus on lungs and bones. The methods for bone are x-rays, as you can see here, on the top left, you have lysis and sclerosis of the bone, you have a Codman's triangle, which you see here under B, on the top left, that's a reactive calcification which occurs when the soft tissue mass lifts the porosity from the bone. And you have spiculae, which you might see here, which are slight lines of calcification in the soft tissue mass. You want an MRI of the primary; you want it for marrow involvement or soft tissue involvement and for relation to the vessels and nerves. For systemic spread, we want x-ray of the chest and you want a CT chest, where you will see much more. And the classical method is a bone scan for bone metastases. Nowadays, people do PET scans and they're at least as efficient maybe, more efficient in detecting bone metastases. So, either one will be a good choice at the moment. So, what do you do now? You'd find it a little equivocal lesion upon your chest CT and it does not change until the end of treatment. Is that a metastasis? Has time shown you that it's none? Let's take a look at this. So, is imaging sensitive and specific? The best paper about this is from around the millennia. It's a paper by Picci from Bologna, and they looked at 81 patients, who were suspicious for having many metastases upon the imaging and at surgery 29 of those had metastases and 22 had none. Now, they try to find factors which predicted if those changes upon imaging were real or not real and the only thing which was real was the size of lesions. So, lesions which were larger than 5 millimeters were more likely to be metastases than others, but 10 of the 25 patients who had only nodules below 5 millimeters had metastases, so you're not safe. Variations in number, variations in size during chemotherapy did not tell you anything which is easily explained because your metastases may contain osteoid, osteoid will not shrink even if the lesion is devitalized, it will not shrink. Sometimes, radiographs just tell you, oh, this lesion looks long or thick or whatever. It can't be a metastasis, no, osteosarcoma metastases another paper from Bologna, can have various appearances but not always the round, ossified lesion which you might expect. You might even have cavitations, necrotic masses. So, if you have anything, considered it suspicious. So, in conclusion, chest CT is the best available technique to find lung metastases. It is not very specific of lesions that are less than 0.5-1-centimeter in diameter. Others will, other methods like PET or so will not help you much because a PET specifically will not work in those small lesions. And chest MRI remains investigational, it will not answer the questions. So, what do you do with small

lesions? Take them out, if in doubt, take them out. You will cure more patients by thoracotomies than expected. And just as proof, we've took up this lesion, it was a metastasis, the patient was cured. Now, let's come to the disease in general. There was a very, very famous orthopedic surgeon in the middle of the last century, he said, if you do not operate, they, the patients with osteosarcoma, die. If you do operate, they die just the same. Gentlemen this meeting should be concluded with prayer. So, a very, very grim situation and why is that situation so grim? We have two problems, tumor growth, like here on the left. Well, you can cut that out. Problem two, patients will develop metastases usually, to the lungs and you cannot cut that out. Fortunately, the situation has changed, it has changed because we have chemotherapy, chemotherapy together with surgery and this combination will cure patients. So, what do we do today? We do our imaging, then we do a biopsy to find out if it just looks like an osteosarcoma or if it is an osteosarcoma, afterwards, there's a period of maybe two to three months of so-called neoadjuvant, preoperative chemotherapy. Then, the tumor is taken out and there's another half a year of so-called adjuvant chemotherapy plus surgery of any primary metastases you might find. The chemotherapy you use is based on, globally based upon three to four drugs, doxorubicin, adriamycin, cisplatin, methotrexate in high doses and ifosfamide. What is reached with that? There was a meta-analysis a few years back of over 4,000 patients and if you look at the survival, you see that you have 10 years survival in children of about 66% and then, a little bit lower in adolescents and adults, but still above 60% long-term survival. Of course, if a patient comes in not all have the same metastases and this is from our group, the COSS, Osteosarcoma Study Group of Germany, Austria and Switzerland, about two and a half thousand patients some years back; we found that patients with localized disease had a prognosis survival of about 70%, localized extremity disease. Patients whose tumor was located in the limbs or with primary metastases and those were almost 450 patients, only survived at about 30%. Why is that? It's because of surgery. As you can see here for patients with primary metastases also from our group, you see that patients who had complete surgical remission of primary metastases, so, patients with primary metastases, patients who had complete remissions, over 40% survived and those who didn't have complete surgical remissions basically all died. So, surgical remission is a major thing. Which technique do you want to use? Do you want to amputate? Do you want to do an extremity reconstruction? Do you want to do rotationplasty, whichever technique, you must consider the surgical margins you might achieve and those were classified almost exactly 40 years ago by Bill Enneking, he said you have radical resection, either remove the whole compartment. So, basically, in knee osteosarcoma you do a hip amputation. You have wide resections. If you have an unviolated cuff of healthy tissue around your removed surgical specimen. So, basically, an amputation above the tumor, somewhere in the femur or limb salvage, removing the effected joint and reconstructing it later; you have marginal margins, if you're close to the lesion and you have intralesional margins, if you violate that anywhere during your surgery. And you see here from our German, Austrian, Swiss COSS group, over three and a half thousand operated extremity osteosarcomas, in the early Eighties, most patients, almost two thirds, had either amputations or so-called rotationplasties, nowadays, only about 10% of patients are amputated or receive rotationplasties, the rest has limb salvages. Everybody wants to salvage limb. You live better with the leg than without a leg, you move better with an arm than without an arm but you have certain risks even today. As you see here, the local recurrence rate with limb sparing surgery is almost three times as high than with amputations. Which is not so surprising as you might have a little accident and violate the tumor but after all, the majority of patients, the vast majority is even saved from local recurrences by limb salvage and that's absolutely the majority of patients can receive that. You don't want to have local recurrence. Why don't you want a local recurrence? This is the survival of patients without local recurrence, from a paper by Dr Andreou by our group. So, think twice before you do surgery, you have time, you're doing pre-operative chemotherapy. Find the best surgeon, find the best situation, don't experiment, you don't want your patients to have a local recurrence. Radiotherapy. If you cannot operate, you might want to irradiate and that was done the middle of the last century. Paper from 1955 shows very nicely that the tumor got smaller with radiotherapy. Unfortunately, it grew back after a while and that's what happens to many patients; radiotherapy in the long run is not terribly effective and you see that here, from a paper, meta-analisys of local control rates with radiotherapy and, you see here, to

achieve that they correlated the local recurrence rate and the dose radiotherapy and you see here, to reach 70%, 80% local recurrence free survival, you also need 70, 80 Gray. So, you need very, very high doses of radiotherapy. So, for local therapy, our take-home messages would be operate, operate and operate. Limb salvage is often feasible. You can reduce the local recurrence risk, you don't want a local recurrence, you can reduce it by good imaging, by smart planning, good chemotherapy and excellent surgery or radiotherapy may be an option for selected, very selected inoperable lesions and we have studies with proton or heavy ion radiotherapy ongoing. When do you want to operate? Do you want to operate in the beginning or do you want to operate after some chemotherapy? Does that influence prognosis? Probably not. We have a prospective study of that, by pediatric oncology group, in the 1980s, and we have some retrospective data. So, patients who had immediate surgery did not do significantly better but if you do your surgery delayed, you have the chance to see what your chemotherapy does. How does the tumor respond to preoperative chemotherapy? Like in this slide, do you see a very, very terrible viable tumor in the beginning and at surgery, three months later, your pathologist tells you it's dead. I cannot find any tumor; did you do the right thing? With response, you have a wonderful predictive factor. Usually, tumors which are more than 90% dead are called good responders and you see those here in the blue line, our COSS group, almost three quarters are survivors. Poor response, more than 10% viable tumor, you see the long-term prognosis is below 50%. So, a very, very strong prognostic factor. You've heard a lot about what to do with osteosarcoma, you want to hear these things are getting better. So, are things getting better? That was looked at a few years ago both for Europe and for North America and there you see that things were really getting better in the 1980s or in the 1970s and since then things have sort of plateaued. They were not getting better. We wanted better so, what do we do? We have these four active agents; does it matter how many of those drugs we'll use? And there was a meta-analysis a few years ago of a lot of trials and they showed us that three drugs are decidedly better than two drugs. So, all four drugs, doxorubicin, cisplatin high-dose methotrexate, ifosfamide use at least three and you will have better results. How about if you use all four and that's on the right of the slide, three drugs, the solid line, four drugs the striped line and you see it's absolutely the same. So, it doesn't matter. Your protocol should include three drugs at least. If you want to use four drugs that's okay but would not result in better outcomes, maybe, you can reduce some of the three drugs for toxicity reasons. That's my personal opinion at least three drugs should be used might not really matter which are the three additional, the fourth drug might not improve outcomes but maybe adding a fourth will allow you to reduce cumulative toxicity and optimal, the optimal conventional chemotherapy protocol remains to be defined. Nowadays, everybody is into targeted therapies and modern stuff so, we will probably never learn. Might results be improved by increasing dose or dose intensity of chemotherapy. That was analyzed by an English trial that used chemotherapy with G-CSF or without G-CSF. With G-CSF they aim for two-week interval instead of the conventional three-week intervals without G-CSF. Other chemotherapy was not the most effective, they used the two-drug regimen, doxorubicin and cisplatin, which they don't use anymore but with G-CSF they didn't find any effect, so, don't use G-CSF. How about high-dose chemotherapy? About 20 years ago, 30 years ago there was a big boom of high dose chemotherapy, people treated every tumor with high-dose chemotherapy. In osteosarcoma, like in most cancers, that does not work; in an analysis not randomized but patients who received high dose chemotherapy and patients who didn't, were compared in Italy and Scandinavia and there was no difference but don't use high dose chemotherapy for osteosarcoma unless you want to torture the patients. We have a lot of problems with the poor responders. They have many, many recurrences so, can their outcomes be improved? That's a major question. Maybe we should use a different chemotherapy after surgery, maybe, we should use some more chemotherapy after surgery for the poor responders. If we want to study that, we find that outcome for the poor responders is about 50%, EFS at three years and with a usual statistical significance and power and raising that to 60% you need 700 randomized poor responders. Now only approximately half of the patients will be poor responders, others will be good responders. So, you need about 1400 patients and to have a study of that you need about 2000 patients overall to account for drop-offs, patients who do not want to be randomized and so on. If any country, if any group wants to do that on their own, they would work for decades and that is why many countries, all shown here in this slide, got

together almost 20 years ago now, and formed the European and American Osteosarcoma Study Group, EURAMOS to run this trial. It wasn't an easy running sector, big trial, you have many, many different contracts and rules and so on. You needed to get the drug everywhere, that is shown here on this slide and you have certain complications with GCP, good clinical practice, which gives you a lot of bureaucracy but very little else, safety for your patients. We did that trial in those countries and managed to recruit in about five, six years over 2000 patients from 17 countries, half of them in America, half of them in Europe. What did we do? We registered all patients gave them all the same induction chemotherapy methotrexate, doxorubicin, cisplatin, and operate them. Then, poor responders were randomized to receive MAP or to receive more intensive chemotherapy afterwards augmented by a top inside and high dose ifosfamide that's MAPIE. Good responders who were not deemed eligible to receive such a toxic treatment were randomized to receive the same chemotherapy or interferon as a maintenance treatment for two years. So, let's first look at those poor responders, MAPIE versus MAP. You see the design, another form, were poorest, the largest respondents, who had a complete resection of the tumor, no progression until surgery. When were recovered from therapy, they were randomized to receive either the same drugs to which the tumor had not responded or to receive an additional ifosfamide, etoposide and to prolong this intensified therapy from 29 to 40 weeks. This is what happened, a paper by Neyssa Marina. MAPIE versus MAP. And you see, after two years, identical. Maybe in the first few months, the more intensive treatment was better, maybe, patients on the...were looked at for recurrences after surgery but after two years you see absolutely identical graphs for event free survival but the augmented therapy was more toxic. We had particularly more grade 3 and 4, significantly more grade 3 and 4 for non-hematologic toxicity. And we have more secondary leukemias in this augmented group which is not really surprising if you suddenly start using ifosfamide. So, but conclusion for those poor responders is that adding ifosfamide and etoposide to MAP it's associated with additional morbidity and has no effect on survival outcomes. The modern thing is immunotherapy and we were very modern. We decided we have the good responders so, can we improve their results, by this immune therapy? At the time there was only interferon around that had the correct record as being effective against osteosarcoma. So, we randomized methotrexate, adriamycin and cisplatin alone against that added interferon for maintenance. You see the treatment outlined in the graph, after the treatment was over, which was identical. It was 29 weeks of chemotherapy. We added interferon, pegylated interferon, α-2b subcutaneously until two years after they started treatment with appropriate monitoring tests, supportive care and dose adaptations. We tried to do that, but as you see here, only about three quarters of patients reported starting this maintenance treatment at the end of treatment of chemotherapy even though they were randomized but they were randomized half a year earlier, they thought therapy was about enough, they were tired. So, one quarter of patients didn't even start it and of those who started about one quarter terminated early either because of toxicity, because of progression, because of refusal. This is what we found, in blue, conventional therapy, in orange, the interferon arm, no statistical benefit of adding interferon maintenance. So, in conclusion, the evidence from our trial does not support adaptation of postoperative chemotherapy based on the histological response. So, we have a major, major prognostic factor here. Poor responders will do poorly but we can't do anything about it by changing post-operative treatment. Now, how about mepact, L-MTP-PE? You all know that is heralded by some, especially a company as the greatest thing ever for osteosarcoma based on a trial, a trial by the American groups, at that time they were two before they got together. And what they did is they, at the time, they wanted to study two things. They wanted to study if ifosfamide added anything and have MTP maintenance 48 times after the end of treatment, added anything. And to make things a little bit more complicated they substituted ifosfamide for cisplatin preoperatively, they added it to cisplatin post-operatively. So, it's a bit complicated design. The, A+ and B+ are the arms with this MTP. The Americans published the first analysis and found that adding ifosfamide to standard chemotherapy in this form did not enhance event free survival and they're reported that adding MTP might, might improve EFS, but there was an interaction, an interaction between giving ifosfamide and MTP. So, on the right, you see the very top line, the best ever is Ifosfamide and MTP. The very bottom, the worst ever, was without it. And so, no MTP. And so, they said based on interaction we can't do anything, we don't know. A few years later,

they came out. They didn't find statistical interaction anymore. P is 0.102, so, close and they said, yes we do have a survival benefit of 8% at six years. There was a strong discussion some years back. At the end, MTP was not licensed and is still not licensed in the United States and they got some very nasty comments back from the FDA saying that the results are not robust and highly statistically significant and so on. Surprisingly, the drug was licensed in Europe and it's marketed here. You can buy it if you have lots and lots of money and if you believe in it. Do you believe in it? I don't, I'm not the only one. I think the efficacy data is not sufficient and it's not a part of standard osteosarcoma treatment. So, that was primary osteosarcoma. What do we do for recurrences? First of all, let's look, when do recurrence happen and you'll see here, they usually about two thirds happen within the first two years, particularly, after chemotherapy is over, about 95% happens within the first five years but there are later recurrences and we're currently working on a group of patients who have their first recurrence after more than 10 years. Where do those recurrences occur? You see here, on the left, there are usually metastases, local recurrences only make out less than 5%, sometimes they are both combined. Where do those metastases occur? They usually current in the lungs, sometimes in the bones, rarely other sites. So, like your primary metastases. Is searching for those metastases even worthwhile and how? Well, the overall survival of your patients who have metastases is not good but it's not absolutely dismal. So, you have 23% five-year and 18% 10 years survivors. Those with radiology do better than if the metastases come out, or signs, if your diagnosis of metastases arises from signs of symptoms, usually, though, what we do is we search recurrences frequently very early, when there's nothing we can do. Later, when patients have a good prognosis, a better, let's say, a better prognosis, we look less frequently, when we could do more, and then, we stop after 5 to 10 years which might not be the best idea. Here we see, on the left, osteo-Ewing-sarcoma patients with early recurrences have a dismal prognosis. Those with late recurrences are those who survive. And if you stop your x-rays or whatever you do for screening for recurrences, you will miss this lesion, this group of lesions which arose here in a patient more than 10 years after the initial diagnosis. So, we don't really know when we should stop looking. Now, which method should we use to screen for lung metastases? X-rays? CTs? CTs see smaller lesions. So, we wouldn't have found this one lung met if we wouldn't have done a CT, but it's not very specific. We would not have found, would not have done anything about the other lesions. This is about 10 years old, so, maybe, the radiation exposure is a bit lower by now but then, one CT scan had about 750 times the radiation exposure as one chest x-ray. So, it would probably be, it would have been a better idea to many, many x-rays and to do a few CTs and there's only one randomized study here, it's from India, they looked at 500 localized extremity osteosarcomas at their prognosis, three years from randomization, they randomized between chest x-ray and chest CT and they randomized between six months and three months and they did not find a difference by using chest CT. So, if you do good to x-rays and follow-up it's probably good. If you see anything in your x-ray, you want to do a CT, of course. How should you treat recurrences? Well, you should do surgery, as you see here, and you should do surgery with a complete remission. You don't want to do surgery if you cannot take out your whole osteosarcoma recurrence. How should you do surgery? A few years back, we did a survey amongst experts and collaborative groups and they all did open thoracotomy with palpation. We now have a lot of thoracic surgeons who prefer thoracoscopy, where they cannot palpate. I understand this will be looked at in a randomized fashion against thoracotomy by our American colleagues and it will certainly be very good, at present, I would say still do thoracotomy. Which chemo should we give during recurrence? Is that the right question? No, that's the wrong question. The right question is, should you give chemotherapy at all? We looked at our recurrences, over 500. We did find a slight benefit for the patients with chemotherapy in univariate testing. Of course, the patients who had chemotherapy were selected in a different fashion, they were patients with short intervals and several lesions, while patients with long intervals, with only one lesion, where the local relapse, who had imaging, were prone to have surgery only and patients who had radiotherapy usually had all kinds of negative prognostic factors. If you want to give systemic therapy for your recurrences, what do you do? Well, make your patient participate in a phase II trial so, we can learn something that's the main answer, you might want to use again, if you do not have a trial available you might want to use one of those drugs which are not given, one of those effective drugs which are not given in first

line, you might give ifosfamide/etoposide, carboplatin/etoposide, gemcitabine/docetaxel, topotecan/cyclophosphamide, metronomic therapy. That's sort of chemo, which might or might not work. How about other drugs? There are many, many, many drugs tested for osteosarcoma. This is a paper from some years back, worth to look it until 2010 and you could see many, many, many, many trials, problem, recist does not work in osteosarcoma, recist is based on changes of the diameter of your lesions during effective chemotherapy, they will shrink but osteosarcoma metastases might not shrink, they might not shrink because those lesions make osteoid matrix bone and [Audio Not Clear] totally dead. It might not shrink. So, osteosarcoma had the lowest response rate of any malignancy in pooled, COG American trials. So, we need other outcome measures. Let's look at some modern drugs, targeted therapy. Everybody says, let's target, let's hit those mechanisms which are active in this tumor and we will cure it. There's a problem here, osteosarcoma has many, many, many alterations. It has probably genomic instability so that it will have many, many, many other alterations by the time you do your phase II treatments. Nevertheless, we do have some TKIs which were tested in studies, sorafenib, regorafenib, apatinib, cabozantinib and there is a certain efficacy particularly upon the imaging in stabilizing the disease, stabilizing it for several months, we rarely see responses. Interestingly a Chinese study of apatinib which was published very well, found many, many responses, but I don't know maybe that's because the patients are/were Chinese. But here we have phase II trials of TKIs. You might want to use them in relapse. We don't know if we can use those drugs in first line, that will also be for the first time addressed in this study by our American colleagues. How about checkpoint inhibitors? Osteosarcoma has for pediatric cancers one of the highest mutational loads. So, it might be, you know, mutation load is good for checkpoint inhibitors because less mutations than adult cancers. So, here's phase II studies of checkpoint inhibitors, pembrolizumab and so on, and you see, again, some stabilization basically very, very, very rare partial responses. So, you might consider them, but don't give them if you want to cure a patient, give them if you want your patient to live maybe one month or two longer. So, at present, for all those non-chemo systemic therapies, we have signals of minor activity. Combining those agents with the necessary chemotherapy may be very challenging for toxicity reasons. Translating that into standard therapy has not been done. There has not been a major breakthrough. So, you still do the same thing for osteosarcoma as you did in the Eighties. You don't do anything extra in first line, you might with recurrence, you can operate, you might prolong life for a few weeks to months, by giving second line treatment. No major breakthrough. But the caveat, a whole lot of new drugs is flooding the market, nobody wants to die without having received those and it gets harder and harder to die for bone sarcoma without having been exposed to the side effects of off-label unproven experimental treatments. If you want to change that, support phase II trials, enter your patients onto phase II trials and if you don't have those trials available at your centers send them somewhere, send them somewhere where they do have a phase II trial. Now, we're coming to a conclusion of osteosarcoma. Multimodal treatment, it's the key to success. Intensive chemotherapy is always required, surgery is always required and remains very, very important. Radiotherapy still only has a very selected role in very selected inoperable patients. You want to avoid the recurrences, do everything right, do everything right during first-line treatment. A better understand of tumor biology might or might not help us to find ways to improve survival. If you're treating osteosarcoma patients, if you don't really know what you're doing, look at the bone sarcoma guidelines of ESMO and they will help you guide your patient to his best chance. Well, I'd like to thank you for your attention. Please stay safe.