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The natural history of sarcomas

Prof Casali: Hi, everyone. This lesson is about The Natural History of Sarcomas. It will be a kind of introduction to this online course on sarcomas. If these are the normal tissues and these are the malignant tumors, it's interesting to know that sarcomas are just a small fraction of all malignant tumors, about 1% of them. And so, they are definitely rare cancers. Sometimes, they occur in the framework of a genetic syndrome. But more often, they are sporadic. There are proportion of them, however, which are marked by chromosomal translocation, so, have a simple cariotype. Most of them have a complex cariotype. In general, surgery is, as off today, the treatment mainstay for most sarcomas, if not almost all sarcomas. The clinical presentation is like this. So, it may be, in the very typical case, a soft tissue mass which clearly may be larger. And indeed, the diagnosis tends to be late in several cases such that quite often soft tissue sarcomas do present as large masses. And one of the reasons is that, clearly, there are a lot of benign conditions from the inflammatory to the neoplastic benign ones, for example lipomas, as in this case, which mimic soft tissue sarcomas. And so, on one side is the rarity of sarcomas, and on the other side, the fact that they resemble highly benign conditions is something which inevitably leads to a degree of diagnostic delay. In fact, if sarcomas, as mesenchymal malignant tumors, are very rare, the mesenchymal benign tumors are very common. So, there is a difference by a factor of 100 between the incidence of benign mesenchymal tumors and mesenchymal malignancies. This is the median age of soft tissue sarcomas in GIST. But then, there are some sarcomas which are typical of the child or the young adult. I'm recalling osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, which are very rare. Their incidence is lower by a factor of 10 in comparison to adult soft tissue sarcomas. So, overall, the main entities within the sarcoma family have all an incidence which is lower than 6 per 100,000 a year. So, they definitely meet the criteria of the definition of rare cancers. I mentioned the lipomas but I could also mention uterine fibroids or benign uterine leiomyomas, which are very common. And so, their incidence is so common as compared to uterine leiomyosarcomas that, for example, some treatment's procedures, so like morcellation, been outside and in -bag, is being used also quite extensively. And clearly, is a big problem if the tumor actually is a malignant mesenchymal tumor such as a leiomyosarcoma. So, I mean, these are the problems which are typical of sarcomas and they lead to treatment inappropriateness in a substantial proportion of cases. So, if this is the timely diagnosis of a disease in its clinical phase, the diagnostic delay may occur in sarcomas much more than in any other tumor. On the other side, it's clear that the rarity of sarcomas makes it very difficult to talk about in early diagnosis in the preclinical phase of the disease because the prior probability of sarcomas is really very low. On the other side, the aim is the timely

diagnosis. So, a while ago, in the UK, there was this campaign trying to make general practitioners aware of soft tissue sarcomas when a soft tissue mass is around 5 centimeters, like a golf ball. Which is a little smaller than 5 centimeters. The likelihood that that mass is actually soft tissue sarcoma is quite high. So, as high as to justify something more, I mean, some investigation. So, this was an attempt not to pursue an early diagnosis but a timely diagnosis. But probably, the main problem of sarcomas in general has to do with pathological diagnosis. So, it has to do with the appropriateness of the pathologic diagnosis, so, once a biopsy or even surgical intervention is made, because in the community, there are data across countries which point to one third or so of inappropriate pathologic diagnosis, as long as these diagnoses are made outside the reference centers. Clearly, this is a big problem. First of all, because obviously any treatment planning needs to have an appropriate diagnosis but all the more today that we are much more aware of the discrepancies in the natural history and also in the sensitivity to treatments of different histologists. And so, inappropriate diagnosis is even more important. So, one priority in the care of sarcomas is the first diagnosis, is the appropriateness of the first diagnosis and also, the appropriateness then of the first clinical decision. Because it's the first clinical decision, as it may happens in several tumors, which may make the difference for the prognosis of the patient. And this clinical decision at the beginning of the history of a sarcoma patient needs to be multi-disciplinary. This means that it should involve a surgeon, a radiation oncologist, a medical oncologist and of course, also pathologists, radiologists and so forth. So, multidisciplinarity is vital. And again, it's not easy as long as sarcomas are rare. And so, finding a multidisciplinary team made-up of experts who are all experts in sarcomas, clearly this is not easy outside reference centers for sarcomas. And so, it's crucial to properly refer sarcoma patients to sarcoma expert centers, or to work within a sarcoma network. And the pathologic diagnosis and the strategic clinical decision at the beginning of the patient's history are crucial. Because then, the local treatment which will often be surgical, will be crucial as well. So, centralized referral is the usual recommendation or networking, more and more, even because, being rare, sarcomas don't have so many reference centers. And so, sharing a clinical case over a network, centralizing what is necessary to centralize and then, mitigating however, the health migration of patients is the only thing which makes sense from under the perspective of the organization of healthcare. There are data which point to some improvement in the survival of sarcomas, but also, to differences across countries which clearly may be due to several factors but may also be due to an insufficient quality of care. So, improving quality of care is important. I already mentioned a timely diagnosis. I mentioned the pathologic diagnosis. I must mention the appropriateness of the local treatment. Surgery, in particular. And there is this expression, which is a Whoops surgery. Whoops! is what the non-expert surgeon may say when during surgery, he realizes that it was a sarcoma. And then if, I mean, the surgical strategy was not tailored to a sarcoma diagnosis, it might be too late and the local control, at least, of that patient may become problematic. Probably, the main reason is that you have a pseudo-capsule around the tumor, which may lead the surgeon to believe or to hope that the excision was complete. Indeed, it may not be complete. And, you know, sarcomas, the history of surgery in sarcomas is the history of mutilating surgery. Up to some decades ago, sarcoma surgery was mutilating in most sarcoma patients. Then, at least from the '70s, the '80s, sarcoma surgery has become conservative in most cases. Both because of an improvement in technologies, but also, because of a cultural evolution of surgery, of cancer surgery, which clearly didn't affect only sarcomas, but which affected sarcomas in any case quite strongly. And so, we are happy today not to see so many amputations. However, there are cases, especially when the local control of disease has been ineffective at the beginning, in which as long as the tumor relapses, you may have to do an amputation, even today. So, conceptually, there is a pseudo-capsule and then there is a reactive zone which is inflammatory, fibrous and so on. But you may find some tumor cells there, and so, ideally you should cut outside the reactive zone. And then, there is another area in which you can find skip lesions. And so, you will define surgery as intralesional, marginal or wide, depending on where is the surgical margin. And then, of course, you may resect the whole compartment. So, the compartmental resections, which today are not very common unless the disease is large and sometimes, clearly a sarcoma. Quite often, typically, in several anatomical sites, a sarcoma may be extra-compartmental by definition. And so, even a compartmental resection, or even an amputation may not necessarily be radical.

It depends on the extent of the disease, of course. I would say that today, the aim of the surgeon is to make a complete excision, which, however, needs to take into account the surrounding tissues. So that there are some tissues which are very resistant to the invasion by sarcomas, and there are other sites in which the surgical margin must be wider. So, you need an expert, a sarcoma surgeon, who should be technically approved, for sure. But also, he needs to be aware of the natural history of the disease. And clearly, this is not easy in a rare cancer. Then, you may question to which extent local relapse in itself results into a higher probability of a systemic relapse. You may say that sarcomas, which are problematic from the local point of view are also more aggressive, and so, they may be more exposed also to a systemic relapse independent of the local control. This is a kind of vexata quaestio of the sarcoma literature. But in any case, at least, a re-excision, due to a lack of local control after the first surgery, implies higher costs, but above all, some damage in terms of quality of life. And then, at least, you know, a relapse may be more aggressive because of tumor progression. And so, you might have an upgrading of the sarcoma. So, in any case you have these problems, aside from whether there is a direct, causal relationship between the local relapse and the systemic relapse, which probably is the case. I mean, probably, the early systemic relapses may be due almost to the aggressiveness of the tumor, the tumor's biology. But on the other side, after a few years in which the biological aggressiveness of the tumor has possibly resulted into a systemic relapse, then, possibly you may pay the price also of a lack of local control. And sometimes, in sarcomas, the lack of the local control in itself means a lot of problems to the patient. I said, in terms of quality of life, but also, sometimes, they may have local problems which may even kill the patients, directly affect survival because of the local consequences of a local relapse. So, a biopsy is very important, a preoperative biopsy, which allows you, allows the pathologist to make a sarcoma diagnosis and also a very precise sarcoma diagnosis, so, while cytological diagnosis is generally insufficient. So, that with the pre-operative diagnosis, the multidisciplinary sarcoma board can plan the strategy for that patient which will often involve surgery, but may include also radiation therapy, and medical therapy sometimes even before surgery. And indeed, in soft tissue sarcomas, meaning high-grade, in high-risk soft tissue sarcomas, this may be very important also to improve the local control, preoperative chemotherapy is standard in osteosarcoma, in Ewing sarcoma. So, I mean, there are several cases in which surgery is not the first thing which is done. The natural history of sarcomas is marked by something peculiar, which is on one side of the lack, in most sarcomas, of lymph node metastasis, contrary to carcinomas; but the first site of systemic metastasis, which are typically the lungs, this is more typical of some sarcomas, less typical of others, but lung metastases are highly typical of sarcomas. And then, you may have bone metastasis, distant soft tissue metastasis and liver metastasis, so, these are the main sites of the metastatic disease in sarcomas. So, then, of course, you may have lymph node metastasis. Especially, in some histologies, like rhabdomyosarcoma, or angiosarcoma, alveolar soft part sarcoma, epithelioid sarcomas, as in this case. Or you may have a, I don't know, CNS metastasis, which is very rare. They imply a bad prognosis, but this may be typical of alveolar soft part sarcomas, or glial cell sarcomas, or angiosarcomas. So, also, the staging procedures should be tailored to the histology. And when I said before that the pathological diagnosis is important, it's also because today we are more aware than in the past of the peculiarities of the natural history of some histologies. Well, as I say, the lung metastases are very typical. They are highly typical of osteosarcomas as a first site of metastasis, a little bit less soft tissue sarcomas, but in any case, it's quite common and so on. While some sarcomas which are typical pediatric sarcomas, like Ewing sarcoma and rhabdomyoma sarcoma, there is a tendency to a more systemic extent of disease. However, this peculiarity of the isolated pulmonary metastasis implies that surgery is important also in the metastatic setting, in sarcoma. So, surgery is not important only in localized sarcomas but also, in metastatic sarcomas. At least when there are isolated lung metastasis and this kind of surgery dates back to the 19th century. And isolated lung metastasis, maybe one lesion, maybe couple of lesions or more lesions. And clearly, this makes a difference, of course, because the main prognostic factors for surgery on lung metastases are the previous free-interval which clearly is a sign of the aggressiveness of the tumor, the biological aggressiveness of the tumor, probably. And also, another prognostic factor is the number of lung lesions. So, clearly, the more the lesions and clearly the less likely surgery may be curative. Because in any case, surgery of lung metastasis has

a potential cure, and it may also be an iterative surgery. So, you may have to excise repeatedly lung lesions but it's also obvious that while cure is a possibility the first time, it would be much less a possibility in this kind of iterative surgery. But all the same, surgery may give a free interval after it has been done, which may compare with the free interval which, for example, the chemotherapy may give. So, there will be no doubts about what to do and the free interval will be long and the lesions will be in limited number. But there are several cases in which you may have to choose between surgery or lung metastases or chemotherapy, or whether to combine chemotherapy and surgery of lung metastasis. Then, of course, if the disease is not cured, and surgery of lung metastases is able to cure only a small fraction of patients with good prognostic factors. As long as medical therapies fail, you may have several patients with a widespread lung disease without extrapulmonary lesions. So, this affects just a limited number of patients but the lung disease may dominate the clinical scenario. I mean, this gives rise to a palliative challenge, palliativistic challenge, because it's easier to keep under control, for example, cancer pain, it's much less easy to keep under control pulmonary failure, especially, in a patient without extrapulmonary lesions, maybe a young patient, maybe it was a good performance status. Because quite typically you don't have a deterioration in general conditions in sarcoma patients. So, you don't have the kind of cachexia which is so typical of epithelial tumors. And then, of course, if the disease would've been controlled, the follow-up will be focused mainly on the risk of local relapse and the risk of lung lesions, of lung metastasis. Even because lung metastasis will be, of course, asymptomatic and they may be amenable to surgeries. Then, of course, follow-up will be tailored, this may be a quite typical relapse survival curve for the average soft tissue sarcoma patient. And you see that after a few years you have a kind of plateau. Of course, it will not be properly and rigorously a plateau, but the risk of relapse would be much lower after a few years. On the other side, you will have all the problems which today we call the survivorship problems. And, clearly, sarcomas tend to pose challenging survivorship issues. For example, because there are the pediatric sarcomas which are treated heavily with chemotherapy, radiation therapy and surgery. And so, you will have the later effects of these treatment modalities. In any case, you may have complex surgeries which may leave sequelae, and so, you need rehabilitation treatments and so on. So, the follow-up of sarcomas should strongly take into account the issues of survivorship. This, as said, is a general introduction to sarcoma, I must recall that this may be the main groups of sarcomas. So, you'll have a big group of adult soft tissue sarcomas with several histologies. You have the group of gastrointestinal stromal tumors which have a peculiar natural history. You have the group of the pediatric sarcomas, and so, osteosarcoma, Ewing sarcoma on one side and rhabdomyosarcoma on the other. And then, you have several rare bone sarcomas. We will talk about all these groups during this online course. The main feature of adult soft tissue sarcomas is that you can find them everywhere. And this is the case for all sarcomas indeed. Clearly, you have a big group of limb adult soft tissue sarcomas but then, you have the important group of retroperitoneal sarcomas and so on. And above all, you have dozens of histologies. And so, I mean, the awareness about the complexity of the histological partitioning of adult soft tissue sarcomas is very important for sarcoma clinicians, clearly, we are labeling these entities depending on the differentiation towards which the malignant growth tends to. And grading is very important in general in all sarcomas, and one may say that there is more difference in the treatment approach between a G3 and a G1 leiomyosarcoma than between a leiomyosarcoma and a liposarcoma. But this is not that true today, it's less and less true in a sense, because, as I said, we are more aware of the differences, not only in terms of the local evolution of disease and the local implications, but also, in terms of the natural history of sarcomas as a whole. And also, in terms of their sensitivity, for example, to medical therapy. So, the medical therapy of soft tissue sarcomas in particular is becoming more and more histology-driven. They say that grading is very important in single-celled patient groups with a markedly different prognosis, the grading system for soft tissue sarcomas is this one. You can factor in the grading and some other indicators. And you may provide a prognosis for your soft tissue sarcoma patient which may be quite precise. And clearly, it's very important for the adjuvant treatment decisions because adjuvant therapy has become something to consider also, in adult soft tissue sarcomas in which clearly surgery has been the treatment of mainstay with radiation therapy, as long as a surgery has become conservative surgery. On the other side, today, probably, radiation

therapy is spared in some patients in whom it has been used so far quite extensively. And on the other side, chemotherapy may be placed, also peri-operatively but also, chemo-radiation therapy for high-risk soft tissue sarcomas may be placed peri-operatively with some benefit, most probably, in terms of the systemic control of the disease but also, in terms of local control. Then, bone sarcomas are marked by these symptoms, so, pain and swelling and functional impotence with the risk of pathologic fractures, which are always the problem. So, these symptoms should be very important in driving the general practitioner's attention, even in children. Osteosarcoma is, generally, a high-grade malignancy, marked by osteoid production, which is typical of the metaphysis of long bones, around the knee, particularly, but not only, of course. Ewing sarcoma is more typical of the diaphysis of long bones but not only. For example, pelvic Ewing sarcomas are important. And chondrosarcoma, on the other side, is typically an adult bone sarcoma, is a low or high-grade malignancy with the chondroid matrix, just typical of long bones, but not only. Chordomas are low-grade malignancies of the adult, but not necessarily. Typically, of the sacrum and the skull base. And if osteosarcoma is treated by chemotherapy and surgery, Ewing sarcoma by chemotherapy and radiation therapy but generally, also, with surgery, even if not necessarily. Chondrosarcoma is mainly treated by surgery, but then, there are cases in which you may use also radiation therapy in osteosarcoma. You may use radiation therapy in chondrosarcomas, for example, hadron therapy for skull-base chondrosarcoma. And also, chemotherapy or medical therapy may be used in some cases. And so, osteosarcoma is mainly a high-grade malignancy. Sometimes, it's low-grade, but these are rare cases. Also, sarcoma is a disease whose prognosis has been changed completely by the introduction of chemotherapy in the '70s, 80s, so that the majority of osteosarcoma patients today are cured of their disease. And this applies also to Ewing sarcoma, which is a translocation related sarcoma whose prognosis has been dramatically changed by the introduction of chemotherapy. In the adults, you may have a number of extraskeletal Ewing sarcoma, which are much less typical of children. And extraskeletal Ewing sarcoma, which may arise in several primary sites are very similar or are totally similar, biologically speaking, to bone Ewing sarcoma. So, it is the same disease. And so, the principles of treatment are absolutely the same. And while chondrosarcoma is a low to high-grade malignancy in which surgery is the treatment mainstay, for sure. But for example, mesenchymal chondrosarcoma has some similarities to small round blue cell sarcomas, like Ewing sarcoma, and the differentiated chondrosarcomas may be sensitive also to chemotherapy. While chordomas are low-grade malignancies, which, as I said, are typical at the skull base, and the sacrum. They have a very slow natural history but a proportion of chordomas, much higher than originally believed, may give rise to metastasis even though the local control is the main problem. It is a disease which we have learned to know quite recently in a sense. Also, thanks to global efforts. Surgery is highly challenging, especially, for the obvious implications in terms of quality of life of sacral surgery. Radiation therapy may probably substitute for surgery. There are studies still ongoing on this, and hadron therapies particularly used both for sacral and skull-base chordomas. So, using total-beam radiation therapy or carbon-ion radiation therapy. And also, targeted therapies have some activity in chordomas. And then, I just mention a tumor which is essentially benign like a giant cell tumor of bone. Which actually is a borderline neoplasm because rarely may give rise to metastasis. It may also give rise to the differentiated mesenchymal component, which goes as a high-grade sarcoma. And it is a disease which may be challenging in some cases, I mean, locally speaking. However, it is marked by the expression of the RANKL ligand which is responsible for the giant cells, which are typical of this tumor. And the RANKL ligand is inhibited by targeted glands. So, even for some low-grade sarcomas, as a matter of fact, we are having some targeted therapies and, in a sense, they are even more effective, in a sense, than in high-grade malignancies because, clearly, the lack of genomic instability may imply that secondary resistance is much less a problem. So, I mean that you may use targeted therapy even in some mesenchymal tumors, which are not that aggressive, which may be cured by surgery in most cases. But in some cases, on the other hand, they may give rise to substantial problems especially, in terms of quality of life. Rhabdomyosarcoma is a typical sarcoma of the childhood. It's very rare in adults. I'm talking of embryonal and alveolar rhabdomyosarcoma which are different from a pleomorphic rhabdomyosarcoma, which is an adult soft tissue sarcoma, so, it's a completely different thing. Even rhabdomyosarcoma has been affected by, I mean, has

been one of the trials of chemotherapy in the '70s, '80s, so its prognosis today has changed completely. It's very rare in embryonal and alveolar rhabdomyosarcoma, very rare in adults, but again, it is the same diseases. So, we should try to implement the same treatment criteria which are effective in children. And finally, I mentioned gastrointestinal stromal tumors which up to the '90s were labeled as leiomyosarcomas or leiomyoblastomas or something like that. Today, we know them very well. They are tumors of the gastrointestinal tract, typically of the stomach or the small bowel, also the rectum, for example. Their histogenesis has to do with the interstitial cells of Cajal. Their standard treatment again as of today is surgical and surgery is able to cure most of them. The prognostic factors are very trivial, so, the mitotic grade, size and site. But genotype is important also for the patient's prognosis, but that mainly is a predictor of the sensitivity to targeted therapies. They typically relapse within the abdomen, even though you may have more metastasis per se but you don't have, or very rarely, lung metastases. So, typically the relapse takes place in the peritoneum or to the liver. And these patients may die of abdominal disease. This paper, by Hirota, opened the way to targeted therapies in GIST because of a mutation to an oncogene which is the c-kit oncogene, otherwise, the PGF receptor alpha. And this implies changes to the KIT or the PGF receptor alpha receptor who is a constitutive activation of the tumor growth. And imatinib has been, the most typical, the first targeted therapy which in practice works in chronic myelogenous leukemia and then GIST. So, GIST has had the privilege of being targeted by this model of targeted therapies in oncology. And GISTs are a model today, I mean, even today after more than 20 years after the beginning, are still a model for targeted therapies in so many cancers. Probably, they are the best model. However, with the strong limiting factor of secondary resistance, after a median of two years in the metastatic disease, which means that the prognosis of metastatic patients has been revolutionized by targeted therapies, but clearly, in any case, unfortunately, the prognosis is still marked by secondary resistance. So, we know today a little bit better the biology of these tumors. So, we also know that there are some GISTs which don't have KIT or PDGF receptor alpha mutations. The SDH-deficient GISTs, which are typical of childhood, typical of the stomach, are typically multicentric. But then, we have a proportion of GISTs within the type-1 neurofibromatosis landscape. These are multi-centric, but it was a small bowel. And then, there are others which are marked by other molecular mechanisms. Surgery is crucial in GIST, but adjuvant therapy with imatinib is used when the risk of relapse is significant, sometimes, you need to use imatinib pre-operatively. And then, we have second and third and fourth-line targeted therapies for them, so that the prognosis of GIST is markedly improved. So, in the end, referral is important. Proper referral is important for sarcoma quality of care and as is networking. Proper referral and the networking are important to improve quality of care of sarcoma patients while maintaining the highest quality of life possible and improving their prognosis as much as possible today. Thank you so much.