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Surgery of sarcomas

Dr Gronchi: Hello everybody. In the next half an hour or so, I will be discussing the surgical approach to localized soft tissue sarcomas. Soft tissue sarcoma are tumors that can arise from many different sites of the body. They predominantly originate from the extremities, but also from the trunk wall, retroperitoneum, gastrointestinal tract, including GIST, head and neck, uterus, or other genitourinary organs and other sites. These are just examples on how they could manifest. The first approach to sarcoma is biopsy. So, I will discuss biopsy first and then, surgical principles. And I will focus on extremities and trunk wall soft tissue sarcoma together. And then, because they basically represent the commonest locations and also, because the surgical principles that apply to the extremities and trunk wall were developed for extremities and trunk wall and then, they were extended to sarcomas originating at all other sites. Some specific considerations deserve to be made for retroperitoneum location and therefore, I will separately discuss retroperitoneum sarcomas. So, number one is when to rule out sarcoma, when the patient presents a lump to a general doctor or to a family doctor. So, every time a lump is greater than five centimeters in size at any site or is located deep to the investing fascia, including abdomen and thorax, regardless of the size, a sarcoma should always be ruled out. It's not a common disease, it represents more or less 1% of all the malignancies but in fact exists and it's very important to identify it as soon as possible at its presentation, in order to put... to make a correct diagnosis and also, make the proper treatment strategy. The size is five centimeters, there's the so-called golf-ball rule which was invented by a United Kingdom campaign to increase awareness on sarcomas and all general practitioners, family doctors, were granted a golf-ball key chain to remind them that every time they see a tumor the size of the golf ball, a sarcoma should be considered in their clinic. Of course, in distal extremity, hands and feet, the golf-ball rule becomes the marble rule because the risk of a lump being a sarcoma is also there for smaller lumps. So, what are the differentials? Differentials are, of course, a soft tissue lump is a soft tissue sarcoma, but also metastatic carcinoma, metastatic melanoma, NH lymphoma can resemble, present as a soft tissue mass that is particularly identical to a soft tissue sarcoma. In addition, soft tissue sarcoma is not a single disease and we will be discussing about this repeatedly in this half an hour or so. But they are impossible to be distinguished just on MRI or CT scan. So, this is a myxoid liposarcoma, for example, look like T1 weighted, that's MRI, and this is a synovial sarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma. They are basically very similar one to another. It is impossible to make a diagnosis just looking an MRI. Again, this is a family of different diseases, that are at least 70 different soft tissue sarcoma subtypes, types and subtypes, and therefore, a properly correct diagnosis at presentation is important to get the right

treatment strategy. One size does not fit all. So, how we should we do the biopsy? We do core-needle biopsy that can be performed free hand percutaneously when the patient comes to the clinic where the lump is easily palpable and identifiable or under ultrasound or CT scan, when tumors are located deep to the investing fascia and they're difficult to properly identify, or they lie close to critical structures, like vessels, nerves and so on. So, core-needle biopsy. And it is an easy procedure, very cost-effective, the concordance of histologic type is in the 90% range where it is performed free-hand with a concordance of malignancy grade of 86%. And when it is done under ultrasound, this concordance raises up to 100% for histology and 96% for malignancy grade. It's so important to understand the histology because of the great variability of histologic type and subtype. So, in the retroperitoneum it's the same, so, when you have a retroperitoneal mass, you need to properly assess histology because the retroperitoneal mass can be anything. There are a number of different differentials including of course renal cancers, adrenal cancer, exocrine pancreatic tumors, and also Hodgkin and Hodgkin lymphomas and extragonadal germ cell tumors. So, retroperitoneal sarcoma is not definitely the commonest. So, in our hands is basically when a diagnosis of sarcomas is suspected, even in these cases where there are clinical indications that the sarcoma may be there, the right diagnoses, still 20% of them, are not sarcomas. And there are many differentials, as I said, this is a NH lymphoma, for example, which is typically centrally located. But in this case, where T2 tumors are visually the same, on the left-hand side you see a non-Hodgkin lymphoma and the right-hand side is a leiomyosarcoma. So, it's very important, even here, to perform a diagnosis. Again, differentials here, the dedifferentiated liposarcoma on the left and the germ cell tumor on the right. Or a pancreatic cancer on the left and the leiomyosarcoma on the right. A myelolipoma on the left and well-differentiated liposarcoma on the right. Angiomyolipoma on the left and well-differentiated liposarcoma on the right. So, it's very important even in the retroperitoneal sarcoma to perform biopsy to understand the proper diagnosis, because the strategy depends, of course, on the correct histological assessment. While in the extremity and trunk wall, the use of preoperative core-needle biopsy has been there, has been adopted now by many years, and is recommended in all guidelines, the adoption of biopsy, preoperative biopsy in retroperitoneal sarcoma is a relatively recent thing because in the past there was a fear that by punching this mass, tumor seeding could have taken place or bleeding. But now, we have data to support the systematic adoption of preoperative biopsy strategy because it was clearly shown in retrospective series that this procedure is not associated to a higher-risk of recurrence or death. The risk of seeding is less than 1%, needle tract seeding. And this occurs more frequently when the procedure is not performed correctly. So, if the procedure is done with the coaxial needle and is not performed trans-abdominally, the risk of seeding is virtually nil. So, it's important even in the retroperitoneal to understand which is the proper, the correct pathological diagnosis because the treatment will be tailored then to the histology type and subtype. Again, you can see here the proper approach under ultrasound or CT scan of retroperitoneal mass. The concordance with targeted biopsy, CT-targeted biopsy, of soft tissue sarcoma histologic type is 100%. There's a lower concordance with the malignancy grade compared to the extremities soft tissue sarcoma because in the retroperitoneal one the commonest histologic types is the dedifferentiated liposarcoma which is a very heterogeneous tumor and the most aggressive areas may not be reachable by the needle and so, malignancy grade can be underestimated in some conditions. So, percutaneous biopsy is important. There is a need to assess histologically the tumors before surgery because the strategy may change upon histology and the use of coaxial needle is mandatory to offset the minimal risk of seeding. Then, which is the approach? It is important to understand that the quality of initial treatment is the most important determinant of outcome. These tumors have peculiarities that are very different from epithelial malignancies. Epithelial malignancies tend to have an infiltrative growth patterns that make them clearly visible and distinguishable from surrounding tissue and when you see an epithelial cancer, you have the impression that you need to stay apart from the tumor, you need to take the tumor surrounded by some healthy tissue in order to avoid leaving behind you some infiltrated areas. They do originate from an organ, so, they are often non-anatomic constraints, because the organ is, generally, when it is affected by a cancer then it can be resected. There are no skip lesions outside the organ. And they may give rise to lymph node metastases. These are the typical peculiarities of

epithelial malignancies which may lymph node metastasis that are considered stage 3. Now the mesenchymal malignancies do not have a, often, most of the time, meaning, infiltrate growth pattern, they have a pushing growth pattern. They seem to have a capsule which surround them and separate them from the other normal anatomical structures that lie close to them, which in fact is a false thing. It is not true. There is no separation between the tumor and the surrounding tissue organs. The don't originated from an organ, they originate in anatomical compartments within, maybe, different organs. I mean, in between different organs, and they may have several anatomical constraints. They may give rise to skip lesions. They never metastasize, almost never metastasize, say from specific subtype to lymph nodes. This is the way they look like. You see a mass in the thigh, which is... seems to have a capsule but if this is the tumor, this is called the reacting zone, it's not the capsule, it's a pseudocapsule that we will see in the next slide how it looks like microscopically. And this is the healthy issue around. So, microscopically basically this is the tumor, and the capsule and the reactive zone which contain tumor cells. So, if one removed the tumor along this pseudocapsule, you will always leave behind tumor cells as it is done when you do an intralesional resection of the conventional epithelial malignancy. So, tumors need to be taken out surrounded by a cuff of healthy tissue in order to have a proper resection. What is called in the extent, a wide excision. Radical excision, instead is the resection which is performed removing the tumor and the entire compartment into which the tumor has grown. The closer you are to the tumor, the higher the chance of having local recurrence, of course. So, radical resections are resection with the lowest recurrence risk. Wide resection alone, acceptable and the recurrence is in the 10 to 30%, and then, we will be discussing later how to make a wide resection radical without performing that extended resection by adding other modalities. Marginal resection and intralesional resection are not acceptable because the local recurrence is just too high. In the past, the only radical... you see here for extremity sarcomas, was amputation, and that was the way sarcomas originating in extremities were treated. Then, in the '70s and '80s basically the same time when other similar studies were performed, for example, in breast cancer, it was shown how more conservative procedures, wide resection, in association with the administration of radiotherapy, achieved the same result as radical resection. So, the same, breast conservative surgery and radiotherapy has the same results as radical mastectomy and this applies also to extremity sarcomas. So, what is wide, how is wide in the extremity and trunk wall? How much tissue is to be taken out in order to have a proper resection in the extremity and trunk wall? And then, complement the resection with the administration of radiotherapy in order to minimize the local recurrence. Wide means these tumors spread along the muscular fibers, so, they are different with... according to the different tissues that are considered adequate, depending on where the tumor is. So, the width, the longitudinal width is one centimeter, is five-centimeter, sorry. The axial width is one centimeter. And there are tissues that are called barriers that I'll mention in a minute, that also are considered a strong and adequate margin even if they're not super wide. So, this is an example of a wide resection of a tumor located in an easy place, in the thigh. You see the tumor is this one and we perform a five-centimeter margin longitudinally and one-centimeter margin laterally. And also, the appendageal tumor is completely removed. This one tumor-like close to a barrier, like for example the fascia, like, for example, adventitia over vessel, the epineurium over nerve or the periosteum over bone. Even if this margin is gonna be close, it's gonna be even less than one-millimeter, this margin is considered strongly resistant to tumor diffusion and therefore, strong enough margin to be adequate and therefore, to reduce the recurrence risk. These are just how these margins look like microscopically, these are vascular adventitia over vessels. You see here the bone, the vascular adventitia, here is the vascular bed. These margins are one-millimeter but it's strong and even if the vessel is not removed, it will protect the cervical [Audio Not Clear] from locoregional risk. This, instead, if this vascular adventitia is embedded vascular graft is performed. The same apply to epineurium, if it's embedded, you need to perform a resection of the nerve, in location nerve graft. And the same apply to the bone. So, this is the periosteum, this is the bone completely, but the periosteum has been completely stripped off. You see here the tumor and the periosteum which is negative. However, when the tumor is embedded, or the periosteum is embedded, you perform a bone resection. Because it is very important to avoid the presence of tumor edge at the inked surface. This is very bad because it is associated with a higher-risk of local

recurrence. This is an R2 resection, but this is an R1 tumor at the inked surface. No macroscopic tumor left behind but there's microscopic tumor left behind. This translates into a very high-risk, there's a higher-risk of local recurrence. And local recurrence is very common, it's very typical of these diseases and can be sometimes really, really problematic like in this case. Of course, also, distant metastases exist and they are the most important determinant of the outcome of soft tissue sarcomas located in the extremities or trunk wall. But they can be to the lung, to the liver, bone and soft tissue, but local recurrences are important because there is association between local recurrence and distant metastases that is in part related to the fact that local recurrences express the biological aggressiveness of the disease. And here, this study went to analyze the outcome of patients experiencing a local recurrence after surgery performed under consent or local surgery performed in general hospitals, assuming that all surgeries performed in general hospital were inadequate. And we saw that there was an association with mortality and also, with distant metastases, which was different according to whether local recurrence was following surgery at our institution or surgery at a non-specializing institution. Why so? Because when they followed surgery at the specialized institution, these local recurrences were predominantly an expression of the biological aggressiveness. And therefore, a higher association with metastases was found. When this was not the case, a lower association with metastases was found because these are cancers where the combination of recurrence was related to a higher biological aggressiveness and recurrence simply related to a poor surgical technique. So, it's important to avoid recurrences because they may be associated with distant metastases. And also, because the LR is a proxy of higher aggressiveness and therefore, precedes distant metastases. However, it is important to avoid them also because, in these particular sites, the occurrence of local recurrence may directly lead to death. Like, for example, a proximal, when tumors are proximally located, in this case, then, they may directly lead to deaths. So, 20% of patients affected by extremity soft tissue sarcoma, who undergone a positive margin resection and died of disease for loco-region recurrence without any distant metastases. So, local recurrence at critical sites can directly lead to death. So, it's important to avoid it as much as possible. Finally, while tumor biology governs early-related mortality, microscopic resection margin is the most important determinant of late outcome. In other words, if the patient has not undergone a proper resection, his risk of death after the fifth year is twice as high as the one, he would have if the initial resections were adequate. Which are the exceptions? There are two "positive" exceptions, in the extremity and trunk wall to these rules, the rule of need of avoiding fuzzy markers. One is a well-differentiated liposarcoma, well-differentiated liposarcoma in the extremity and trunk wall does not kill anybody. It's a very indolent tumor, it's very close to a lipoma. With the risk of daily transition of tumor of malignant progression, which is less that 5%. And therefore, at least at presentation, a conservative procedure can be performed. One can observe a marginal excision with positive margins. The other classic exception, the rule of positive margin, is the dermatofibrosarcoma protuberans. The dermatofibrosarcoma protuberans is an indolent skin tumor which is really, well, it can occur anywhere in the body, especially, when it is located in areas that have cosmetic implications. One may accept more conservative procedures limiting the margins and those accepting some positive margins because for classic dermatofibrosarcoma protuberans the risk of recurrence is still low. It doesn't exceed 10%. Conversely, the more aggressive variant which is quite rare and is called fibrosarcoma DFSP, should be considered a conventional sarcoma and positive margins are not accepted because in this specific case, the risk of recurrence is as high as the one we have in all other sarcomas. On the other end of the spectrum, the negative exception in extremity and trunk wall is myxofibrosarcoma. Myxofibrosarcoma is a tumor which is very difficult to treat, unluckily. It is very difficult to assess clinically and radiologically which is the real extent, the true extent of the tumor because it tends to expand around the fascial planes. It has a lot of tails, so-called tails. So, diffusion of the low-grade component along the fascial planes. And therefore, it's difficult to achieve negative margin resection. It's more difficult as compared to sarcomas of other kinds. And so, it is the tumor where we basically say that they are never wide enough. If you're not wide enough, if the margin is between zero and one-millimeter, the risks of recurrences are higher as compared to sarcomas of all other kinds. In general, the other sarcomas have a recurrence risk which is below 5%, let's say between 0 and 6 to 7%, while myxofibrosarcoma and vascular sarcoma and malignant peripheral nerve sheath tumor

are the tumor with the highest recurrence risk. Malignant peripheral nerve sheath tumor because can spread along the fiber of the nerve. So, it is important have a wider margin at the nerve levels. So, we said, five-centimeter along tumor margin on the mass. And it should also be five-centimeter on the nerve to try to avoid a positive margin on the nerve stump. Same apply to vascular sarcoma. So, sarcoma originating from vessels, like leiomyosarcoma. This is the great saphenous leiomyosarcoma, it's quite difficult to obtain a wide margin here, but it's important to bear in mind that you need to have one. Because the tumors can spread along the vascular wall. So, I was mentioning initially, now what can we do to upgrade quality of surgery? Is it all about surgery or there are other modalities that can complement surgery and allow a more limited resection to spare function and maximize the outcome? Yes, they are there. This is an example of a myxoid liposarcoma that we're showing you where there is this proximity with the sciatic nerve where a wide excision would require the sciatic nerve correction, where excision would require the sciatic nerve resection. However, we know that radiotherapy can complement surgery, as I already mentioned some minutes ago. And can obtain a better local control compared to surgery alone. These are the two other studies that were performed in the '90s. Which show this and are the bases of the standard approach to sarcoma today. So, sarcomas of intermediate and high-risk are usually treated by a combination of wide resection and radiotherapy. When radiotherapy is given though? In the preoperative or postoperative setting? A study was performed at the beginning of the 2000, which showed that there was no difference in terms of a local control between radiotherapy giving perioperative or postoperative. However, there was a difference in morbidity. So, preoperative radiotherapy has less morbidity in the long-run. A little bit more morbidity in terms of wound infection but less morbidity in the long-run. But most important, preoperative radiotherapy offsets much better the negative prognostic impact of an R1 resection compared to postoperative radiotherapy which in fact does not. These results, these data, didn't come from the randomized study which had a very limited proportion for R1 resected patients, a limited proportion of R1 resection. This data comes from many retrospective observations that are all consistent and show that marginal excision does not affect local outcome after preoperative radiotherapy. This one was a US series, this is a Canadian series, where they clearly show that the planning in advance positive/close margin does not compromise local control as long as all others are negative and preoperative radiotherapy is delivered. You can see here how it is performed. And you see here that also in the same study, they were able to look at the outcome of patients who had a positive margin over a critical structure and they compared to that the same to a similar cohort of patients who instead have those critical structures resected. So, weighing the positive margins where the critical structure is present, but radiotherapy is given, doesn't matter whether the structure is then resected or not. In other words, if you can have a positive margin in the adventitia, you can still leave the vessel intact. You don't have to resect the vessel, if you're given preoperative radiotherapy. So, radiotherapy can upgrade the quality of your surgical margins. Radiotherapy can also be combined into conventional chemotherapy; this is tolerable in extremity and soft tissue sarcoma and it has been proven several times. Any in patients who have a high-risk of recurrence, the combination of chemotherapy and radiotherapy may be of help, for example, synovial sarcoma, undifferentiated pleomorphic sarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, also myxoid liposarcoma, this combination is very effective and is able also to upgrade the quality of your surgical margins and make a focal positive margin as a negative one. In a myxoid liposarcoma, there are either possibility, you can combine trabectedin and radiotherapy. Now, we are starting also the use of neoad therapy and radiotherapy in some histology cancers in order to see whether we can improve further these results. Predominantly, in term of disease control, general disease control, not in terms of local control, because local control in our hands now is in the 95% range with all these adaptations and multi-modal approaches. Should radiotherapy be given to all sarcoma of the extremity and trunk wall? Actually, the answer is, well not really. If anything, in the past there has been a wide use of radiotherapy, now there's the other too that we can spare some patients from the use of radiotherapy and in our hands basically it is given in no more than 40 to 50% of the cases, we definitely consider also histology type, to factor histologic type into the decision but in myxoid liposarcoma, myxofibrosarcoma, vascular sarcoma, those are solitary fibrous tumors among those who have the highest sensitivity to radiotherapy and therefore in this specific case,

radiotherapy is more frequently used. So, it should be given whenever preserving function is a goal and if so, should be given in the preoperative setting. It should be given in selected histologic types and subtypes. However, it may be spared if margins can be wide enough as I was alluding to at the beginning, so, when the margin can be at least five-centimeter longitudinally, one-centimeter axially and stromal bodies are not invaded. So, this is an example of a high-grade myxoid liposarcoma. We calculate the risk and in this specific, by using a very nice tool, which make very handy the use of a nomogram, which is probably of some five years ago, for soft tissue sarcoma extremity and trunk wall. So, in this specific case, the risk of death in this patient was in the 30% rate with a 40% risk of distant metastases. The aspect quality of surgical margin, as I said, here there was the proximity to the sciatic nerve, and therefore, in this specific case, given the high metastatic risk and the expected marginality towards the setting, we combine modalities to maximize the outcome. By doing so, in these 30 years, we have observed a progressive improvement in local control, you see here from basically almost 20% risk of recurrence to where this is actually the...no this is recurrence, to a 5%, 10-year local recurrence risk. These are distant metastases and this was a campaign to also improve the survival. Why so? Because of better local control and overall survival in the last 15 years was basically due to an increase use of preoperative chemo and radiotherapy in a selective situations and high-risk situations. And this improvement in local recurrence has also reduced the overall metastases over time. Finally, what is wide in the retroperitoneum. So, we have been discussing so far, the principles of surgical efficacy in extremity and trunk wall sarcoma. How this apply in more difficult space like the retroperitoneum where basically the microscopic margin assessment is specially for the commonest histologic type which at this site is liposarcoma, is non-sense. You see here now how many multiple structures they touch. Well, we apply at this level the concept that I alluded to some few slides ago of planning in advance some positive margins without compromising local control. Which does this comes through? Because it's minimizing marginality. So, apply type of surgery which is not this one simple excision but it is a tentative wide excision, like the one we do here in the popliteal fossa sarcoma, we do the retroperitoneum. How can this be applied? By performing resection of the tumor surrounded by the adhesion organs. Which are the adhesions organs that are more commonly involved in the retroperitoneal sarcoma? Ipsilateral nephrectomy and ipsilateral colectomy. So, ipsilateral nephrectomy and colectomy of a T4, the resection of the source and mass of the retroperitoneal sarcoma. This is also often performed. While on the left side, left pancreas and spleen are involved in 50% of the cases on the right side, the head of pancreas and duodenum are very rarely invaded and resected. Vascular resection in 13% of cases, 5% in non LMS. So, this surgery is complex but is now being well-described and is very recognizable in 6 stages. It requires multiple surgical skills, but is possible and for this kind of surgery is able to achieve an adequate, a much better local control compared to the past, so much better. So, this approach has shown to have the risk of local recurrence, between 40-50% to almost 90% and increase survival by a 20%. Also, the retroperitoneal sarcoma, also not a single disease, is a family of these types of diseases that includes liposarcoma, leiomyosarcoma, and by the way, also, the liposarcoma type there are two subtypes, leiomyosarcoma, solitary fibrous tumor, malignant peripheral nerve sheath tumor, UPS and others. Locoregional recurrences are the leading cause of death of liposarcoma above all histology types, and the surgical approach should be minimizing marginality. The policy has obtained a 20% gain. in liposarcoma local control, both well-differentiated and de- differentiated, you see it here on the left-hand side the outcome of patients undergoing extended resection; on the right-hand side, the outcome of patients going with gross excision so, basically, simple excision, removal of the tumor without additional tissues. So, basically what in the extent would be a marginal regional resection. You see how the local recurrences are in well- differentiated liposarcoma, 18%, 40%. And in the dedifferentiated liposarcoma 40%, 60%. The others histology types have a low recurrence risk and high metastatic potential. For a leiomyosarcoma you don't need to perform the same resection that you perform with liposarcoma for a number of reasons. One, the reason is that the local recurrences [Audio Not Clear]. And the second reason is that the pattern of growth for leiomyosarcoma it's different from the one on liposarcoma. So, liposarcomas in the retroperitoneum are made by different components and the well-differentiated component is visually indistinguishable from the non-differentiated. So, in order to perform the complete clearance of the well-differentiated component,

one needs to go forward with complete clearance of the ipsilateral path and therefore, this clearance of the ipsilateral path requires resection of at least the kidney and of the ipsilateral cord. Conversely, leiomyosarcoma do not need to be resected in this way. You don't have to give up to the idea of minimizing marginality of performing minimized resection even if you don't perform close organ resection. In this case, the liposarcoma vena cava, the kidney, the uterus could be spared despite what we find that the tumor was removed surrounded by a cuff of healthy tissue. Muscles in leiomyosarcoma of the retroperitoneum originates in the vena cava or vessels, 40% from vena cava, but they can also originate within the renal vessel, rear vessels or other vessels. And surgery may require vascular resection. Solitary Fibrous Tumors, instead, tend to be more indolent and surgery usually is much more straightforward. This is an example of a solitary fibrous tumor on the legs and the de- differentiated liposarcoma, on the right. And this is just to show you how different the approach is even if they look basically...they look different, but for example, the kidney seems more compromised by the solitary fibrous tumor compared to the dedifferentiated liposarcoma. You see here, that in the dedifferentiated liposarcomas despite the fact that the kidney was all pushed above, it can be spared. While in the dedifferentiated liposarcoma, we should consider that this is, all this, apparently normal retroperitoneal fat surrounding the kidney and therefore, the proper approach includes resection of the psoas and the kidney, and the tumor all in block. In malignant peripheral nerve sheath tumor, tumor originates from completely different spaces, so, the approach is totally different. They originated peripheral nerve. And the psoas, so, you don't need to perform in general all the resection. This is a tumor line on the right side, this is the left line, this is an incision over the iliac crest, exposure of the psoas and the tumor, these are the vessels, the nerve vessels, and this is the specimen of the psoas, the tumor, and the tumor nerve which was the origin of the tumor. Some other specific locations like the pelvis, where in the pelvis, solitary fibrous tumors have the common histology type. Followed by leiomyosarcoma and liposarcoma. The pelvis is even more complicated as a space compared to the retroperitoneum, there are multiple critical structures, however, usually tumors tend to be resected with only the rectum and the vesicorectal pouch. However, depending on where they are, they may need more extended or less extended procedure. Finally, there are tumors also originating in the psoas muscles. They are still considered the peritoneal muscles They are treated completely differently, like, for example, well- differentiated liposarcomas, or the ones called atypical lipomatous tumor of the psoas muscle which behave as the same diseases. Occur in this entity, as I said, at the beginning of the presentation, this type of tumor will not kill anybody and can be treated by a simple excision. Conversely, undifferentiated pleomorphic sarcoma, originating from the same psoas muscle are much more aggressive tumors and require multi-modal therapies and resection of the psoas muscle. However, here, again, don't need to resect organs because the tumor originating from the muscle remains inside confined to the muscle. What can be done in the retroperitoneum to upgrade the quality of surgery from marginal to wide? Even here, radiotherapy has been studied for many years, not formally though all studies performed in radiotherapy in retroperitoneal sarcoma were retrospective. This is one of the largest. They tended to show some benefit in radiotherapy in survival in the local control, here is in the liposarcoma group, a large retrospective study on the liposarcoma but a randomized study was performed only in the recent years and was recently published. The randomized study didn't show an overall benefit, but it did show a benefit, I mean, an overall benefit, I mean, benefit in the overall population of retroperitoneal sarcoma but a benefit in the subgroup of liposarcoma was in fact present. Why so? Because liposarcoma is the histology type which recurs the most, where we expect radiotherapy may exert the largest benefit. We then combined also the in-trial and off-trial patients, treated by the same participating institution, the same institution participating in the randomized study. And we showed that this combination of cases, these combined series confirmed what was seen in the randomized studies. So, a benefit in the well-differentiated low-grade dedifferentiated liposarcoma, lack of benefit in highly dedifferentiated liposarcoma, because, as I mentioned few slides ago, the histology type is also associated with the recurrence in this histology type is predominantly distant. So, histology types recur in most of liposarcomas. But in the liposarcoma, a subgroup, there is a subtype, which is higher the division than others sarcomas, which has high disabilities compared to leiomyosarcoma. In both, leiomyosarcoma and high grade dedifferentiated liposarcoma Data showed to have

any benefit from the administration of pre-operative radiotherapy. So, there should be others tools. And, of course, there are specific considerations to be made for specific histology that were not addressed in STRASS. The STRASS is a randomized study; for example, in the solitary fibrous tumor, where we know that radiotherapy is active. I have already alluded to these discussing extremities of tissue sarcomas, so, the solitary fibrous tumor is sensitive to radiations. Therefore, its sensibility should be a big factor in treatment strategy when a solitary fibrous tumor is present. Or when sarcomas are attacking, for example, the spine. So, when the tumor mass is located in a place where there are surgical issues, when it is of borderline resectability, we want to preserve structure. Radiotherapy needs to be considered even if formally cannot be always indicated. So, it should be considered whenever the tumors are of borderline resectability, in well-differentiated and intermediate grade dedifferentiated liposarcoma, it should not be considered in high grade dedifferentiated liposarcomas and leiomyosarcomas. And it can be possible in others subtypes if they're not to be sensitive. What to do then in, for example, in leiomyosarcoma, or high grade dedifferentiated liposarcoma? Well, we can consider chemotherapy, like in this case, or in this case, chemotherapy because we want to reduce the metastatic risk. But whether this is, in fact, a successful policy. So, whether the use of pre-operative chemotherapy is really able to improve the outcome of high grade dedifferentiated liposarcoma or leiomyosarcoma is today not known and is the subject of a randomized study which has just started in Europe and has now recruited some ten patients. So, multidisciplinary discussion is the key, it is the key to maximize the outcomes, because it helps designing for the single patient, the best treatment strategy, which put together all the available evidence, that comes from mathematical studies and experiences. But you saw in our retrospective, in our series of retroperitoneal sarcoma we also observe similar to what we observe in extremity. A progressive improvement in survival and local control in distant metastases control. So, in summary, local control is important for achieving cure, this is all the truer for tumor located at critical sites. You need to personalize the strategy to histology, site and patient. Multimodal is critical to maximize the outcome. So, thank you very much for your attention and have a nice day.