Speaker 2

Speaker Key:

AD Angelo Paolo Dei Tos

Time code	Speaker	Text
00:00:11	AD	Hello everybody. I'm Paolo Dei Tos. I'm a pathologist and I will try to summarise with you what we think is remarkable in terms of sarcoma pathology in, what was remarkable in 2020.
00:00:31		This is my slide of shame, as you can see here, and that's it. Quite obviously, what is really, really to be reminded since 2020 is the new WHO classification. I've been part of this process for approximately 20 years.
00:00:56		It's a pleasure to be still involved over the process of shaping the way we classify soft tissue sarcomas in general, but in reality all the mesenchymal tumours of soft tissue and bone. Why do we need classifications? Pathologic classification represents the variation of the clinical decision making because we have to deal with prognosis, with traditional response.
00:01:25		I always try to remark that conventional morphology is still a powerful tool, but it's true anyway that we are increasingly integrating since 20 years now, like microscopic observation with both immunohistochemistry and increasingly with molecular genetics. Sarcoma classification is actually based on morphology, but it evolved through this progressive inclusion of other techniques. The major aim is to recognise entities that are morphologically and clinically distinct.
00:02:02		We have many, many changes since 2000, like definition of tumour category, the fact that genetics is so much implemented in the classification. Very trendy neoplasm, like malignant fibrous histiocytoma and hemangiopericytoma were totally abolished through the years. A new entity of course has been introduced in the classifications.
00:02:26		One of the good things across the different WHO classifications is that, as an example, gastrointestinal sarcoma tumours are covered by the same authorships and in this way, whatever you take, the GI tract vesicle or the soft tissue vesicle, you will get exactly the same information with on major discrepancies. Also, new categories are coming in, like the entirely new category of

Time code	Speaker	Text
		undifferentiated round cell sarcoma with many different labels inside.
00:03:00		Also, the introduction of NTRK-related lesion as an example of emerging entity. Some of the changes actually are due to the use of new technology, like massive parallel sequences, also known as next generation sequencing, and this is a quite powerful technique with a broader range of applications. For example, validation of a classification, to think of the entity called a pseudo-myogenic haemangioendothelioma, identification, new diagnostic marker, just think of STAT6 in solitary fibrous tumour.
00:03:34		Even identification of new tumour entities like CIC or BCOR, NFATC2 sarcomas. Then somewhat elucidation of sarcoma pathobiology, but also identification of new potential targets, like was the case with NTRK, NGS and of course MIA [?], the other tumour entities.
00:03:57		One of the nice examples is the so-called Ewing family of tumours. A few years ago we were puzzled by the fact that some of the Ewings didn't look actually like Ewing and we called them atypical. But the reason they didn't look so much like Ewing, they were not Ewing at all. Then, what happened is that the group of Christina Antonescu found first these translocations, a new translocation, a group of round cell sarcoma that they called CIC-DUX4 fusion or CIC-rearranged sarcomas.
00:04:33		Since then many more cases were collected, so now we know in some details the clinical pathological features of these entities, like the fact that it tends to occur mostly in, it's likely to show a male predominance and you can see the peak of incidence in the third decade and far more common in the soft tissue, even if we describe the first cases in bone.
00:05:00		Then, of course, you can see the trunk more common, than the limbs and in the viscera and, as I mentioned, Ewing bone is very, very rare. Actually, the morphology is very variable. Heterogeneously you can have, of course, a round cell morphology, but some cases actually show spindling or a petaloid feature, myxoid change. But what is important to say is that all these entities more or less have a CIC rearrangement with a variety of possible partners, like FOXO, like DUX4. Most of the time it can be also FOXO4, LEUTX and so on.

Time code	Speaker	Text
00:05:36		This is just a morphology to show some examples on here. On the left side, round cell component. You can see here the mixed cell features. Pathologists may appreciate these very bizarre cells that you will never see in a Ewing. It's very rare to see in Ewings. But some of those cases, actually in the petaloid morphology some of them can show spindling, which is quite interesting.
00:06:03		Because these neoplasm are still embedded into a group of round cell sarcomas, but actually many of them are not round at all. CIC sarcoma actually have a quite specific immunophenotype. You can see CD99, which is the typical marker of Ewing sarcoma, tend to be very variable and patchy, and this would tend to exclude in principle the possibility of Ewing.
00:06:31		WT1 and ETV4 are relatively often positive. This can help. On the other side, a quite kind of new Ewing marker called NKX2.2 tend to be negative. So, immuno also can be really helpful in arriving at the correct diagnosis. From the molecular standpoint, in addition to the CIC rearrangement, you can have this variation, like for example CIC-NUTM1 sarcomas.
00:07:02		Of course, this is an area not so easy to define because, okay, you can believe that this actually represents a variant of a CIC sarcoma, but the people who first reported NUTM1, I'm referring to Chris French in Boston actually, they also reported this case and they may think it's actually a variation within the group of the NUT-rearranged sarcomas.
00:07:29		In particular, when dealing with new gene fusions and so on, the way we define the specific tumour entity of course needs to be refined in the future. The second example of this group is the so-called BCOR-rearranged sarcoma. You can see, male predominance, peak in the second decade. More common in bone than in soft tissue. Again, ironically, most of these cases actually show a spindle sub-pathology.
00:07:58		They can be a round cell, but many, many times are actually spindle. Of course, they do express BCOR in cyclin B3. Immunophenotypically this is what you see under the microscope, so it's nuclear expression of course. The basic question is, okay, but do we really care to split apart these undifferentiated round sarcomas? Why don't we let them be in

Time code	Speaker	Text
		one gigantic basket, so typically Ewing undifferentiated round cell sarcoma?
00:08:29		Well, if you look at the survival, of course, then you understand why. BCOR does far better than Ewing and CIC and so that's why it's important to recognise that. Moving on to the new target. Well, a few years ago we were so lucky to find NTRK fusions in so-called Wild Type GIST and other times we didn't have any idea that this would have been then exploited therapeutically.
00:08:55		Actually, we know where we are now with at least two compounds able to target and track fusions. Of course, these series are strongly enriched by paediatric cases because these type of fusions are actually seen mostly in these type of patients. If you don't consider infantile fibrosarcoma, which is well characterised with ETV6 and NTRK3...
00:09:26		Actually most of these new entities, mesenchymal entities which are involved in tracking gene fusions, actually the gene involved is NTRK1 and more rarely NTRK2. So, forget infantile fibrosarcoma. The two new entities which you will be finding in the new WHO, it's like the fibromatosis like neural tumour, a tumour that closely resemble peripheral nerve sheath tumour. This is on your left side.
00:09:55		You see LLNT, which pretty much is similar to lipofibromatosis, which is a benign condition, but can reach, can attain a large size, can be locally destructed. In principle, to have a drug that can downsize this lesion that can be really huge, is a good thing. The other one, the tumour resembling peripheral nerve sheath tumour, well, there is a heterogeneous group of morphologies starting from benign, ending up in high-grade malignancy.
00:10:28		Again, you have to remind that these are exceedingly, exceedingly rare. What is good for them, it is a combination immunophenotypically of expression of S100 and which is a neuromarker, NCD34, and in addition of course expression of NTRK. Then, of course, whenever you find this type of immuno profile, you may like to confirm molecularly the presence of the fusions.
00:10:58		This new thing called NTRK, that we need to remember, because it's a clearly new thing, are extremely rare. Remember that infantile fibrosarcoma are anyways most of the time treated

Time code	Speaker	Text
		with conventional drugs and all radiotherapy and it responds pretty much. You have to consider the immuno, that you're going to see like ten cases of infantile fibrosarcoma per year, and out of ten probably would respond very, very readily to conventional therapies.
00:11:32		The other subtypes most of the time are benign, not clearly defined, but certainly represent an area in which you may use, you exploit NTRK as a therapeutic target. As anyway, the detection of this tumour is not easy. Pulling together sarcoma community, we try to set up some kind of expert recommendations which in a way points the technique you may use.
00:12:01		Of course there are many issues related to the technique because in terms of cost, in terms of availability. So, basically what we consider now is that immunohistochemistry represents a good screening test. In the case of sarcomas, if the screen test is positive, then you have to go for a molecular technique and you are free to pick up the one you prefer. Of course, MPS is the one who we'll provide more data.
00:12:31		Of course, one of the issues is that, okay, we have many, many new sarcomas with new translocation, with new gene fusion. Also, we have a small series, one case, two case with novel fusions. This type of granularity, in particularly in absence of clear clinical data, in my opinion, can lead to some kind of confusions.
00:12:58		Particularly if you consider that actually, as brilliantly showed by Felix Mitelman and the other colleagues from Sweden, actually the more NGS used, the more fusion you find, and many, many of them, most of them are actually stochastic events, so they're not drivers at all, they're just passengers. We need to be very careful when we decide to define an entity based solely on a genetic fusion.
00:13:27		That's why with Paulo and Allesandro we try to also to reasonably debate in our clinical sarcoma research journal how we actually need to define an entity, which is an open question for all the sarcoma community. Because the question is, should we forget about morphology, jump on basically NGS-driven type of approaches?
00:13:52		Well, if you look at the first data which has been in a way produced, it does sound like the results would indicate the need

Time code	Speaker	Text
		of a changing of practice actually. If you look at the other nice paper from our French friends, in a way they suggest that molecular profiling should not be used in routine practice, but certainly you want further explorations in the context of clinical research.
00:14:26		The conclusion here, soft tissue tumours still represent a global challenge, in particular diagnosis and treatment, because of their rarity, because of the interest in the difficulty. Rarity certainly affects diagnostic accuracy, so we need to tackle this issue. Molecular testing, of course, is very useful in contexts of morphology. In particular, when we have an entity the name of which is determined by the molecular genetics, we need to prove the existence of molecular genetics if we want to use that specific label. This is my personal position.
00:14:58		On the other side, I think the excessive molecular segmentation can be potentially confusing, particularly when we lack significant clinical data. In any case, the WHO is something we will remember from 2020, we will be remember for a while I think. The WHO classification is certainly crucial to improve the quality of pathological diagnosis. This is the end of my talk. I wish to thank you for your attention.