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The epidemiology of sarcomas

Dr Trama: Good afternoon to everyone. As I think we have understood during this pandemic crisis, the epidemiologists are those that assess the impact, the burden of a disease across population and over time, and this is what I'm going to do today about sarcomas, which, of course, are not virus, but are a type of rare cancers, for which to find epidemiological data might be a challenge, as I'll show you in a moment. I am an epidemiologist and I've always based my presentation on a population-based cancer registry because cancers in comparison to other types of diseases have registries with a long experience in data collection and registering and registration. Population-based cancer registries are entities that basically collect data on all new cases of cancer that arise in a well-defined population, so, they are completely unbiased. They have a major advantage, which is the completeness of the incidence of the cases, and of the follow-up. That's why these types of data sources are used for epidemiological descriptive analyses, which are related to the definition of the incidence and survival of cancers. The problem is that because they have to identify all the numbers of new cases in a geographical area, they cannot collect a lot of information, so, they have a limited set of demographic and clinical data. However, not all cancer registries have few information. This is the example of the Belgian Cancer Registry, which covers, just to give you an idea, the entire population of Belgium, and they basically rely on different data sources, such as the pathological labs, the hospital discharge, but also, the MDT meeting results. So, there are, anyway, cancer registries that of course are able to contribute also with clinical data, so, the situation is very heterogeneous, but cancer registries are wide spread, as I was telling you, specially, in what I would define the Western World. A little bit less in other continents, although, the Southeast Asia is currently working in increasing a lot their population-based cancer registry. But in Europe, we do have a long-lasting experience in terms of cancer registration, and as you can see, we have many cancer registries across European countries. That's why I'm focusing my presentation on these types of the data sources. However, which is the problem, why I started my presentation saying that is a challenge to find data on sarcoma. Because the common statistics that are provided by cancer registries are based on topography on the international classification of, this is for oncology, the topography codes. This is the example of a very useful tool, I always recommend everybody to visit, that is provided by the International Agency for Research on Cancers, and you can see that by different sites, different tumor site, that we have a number of cases, crude and age-adjusted incidence. However, as you can see here, it's impossible to find data on sarcoma. Why? This is not due to the fact that a coding does not exist for sarcomas because, as I was telling you, the International Classification of Disease for oncology do have topography

codes for sarcoma. This is the C49, which anyway corresponds to the connective soft tissue tumor. So, not all sarcomas. This is important to know because the other sarcomas, those that arise basically in different organs, in different viscera, are included in the topographical site. That's why, if we want to have a clear idea about the incidence, prevalence, survival of sarcoma, we need to pay attention to the paper that we read and to the methodology to see really what type of sarcoma these papers are referring to. Just to show you the relevance of understanding which sarcomas are included in a paper, this is an old paper published using the SEER data. SEER is the, everybody knows, is the institution that basically provides population-based cancer registry from the US, and it's a database publicly available, so, lots of epidemiological data comes from the SEER. And what Toro and colleagues showed in this paper is that when we look at the incidence of soft tissue sarcoma, only the C49, I showed you the code, I show you in the ICDO classification, you can see that we end up with an incidence rate of 2.4 per 100,000. When we include the sarcoma across all the other sites, we add another 2.6 incidence rate, and this is important just to show you how much you could underestimate the incidence of sarcoma, thinking that the soft tissue incidence provided in some papers corresponds to the overall incidence of sarcoma, because basically to properly provide the incidence of sarcoma, we really have to consider the different histologies of sarcomas, which I'm sure you know, are quite a lot because soft tissue sarcomas are very heterogeneous group of tumors. They may arise everywhere, and that's why to provide the correct information, we need to pay attention that all the different histologies are counted across the different site where a sarcoma may arise. And that's why also Toro and colleagues showed, basically in the United States, the incidence for soft tissue sarcoma is around 5 per 100,000. So, pay attention because to find epidemiological data on sarcoma is much more difficult than for other countries where you can go to the Global Cancer Observatory and find easily information for sarcoma. You cannot find this information in the routine statistics, and you need to pay attention to what has been published in different papers. That's why in Europe, two specific projects, RARECARE and RARECARENet, who are supported by the European Commission to provide data on rare cancers. Sarcoma is a rare cancer because I showed you the soft tissues sarcoma has an incidence lower than 5 per 100,000, and rare cancers are those with an incidence lower than 6 per 100,000. Rare cancers, of course, are difficult to diagnose, are difficult to count because to properly count them we need robust data, so, we need big database. And that's why these two projects, based on a collaborative project named EUROCARE, which is basically collecting data from the different cancer registries available in Europe, is able to have a big database, a very robust one, and so, this database was used in the previous national project to provide data on sarcomas. So, we basically use these data to show you which is for example the incidence of sarcoma in Europe. And as I showed you in the paper by Toro et al., also in Europe, basically, the incidence of soft tissue sarcoma is 4.7, so, around 5 per 100,000, whereas the incidence of bone sarcoma is much lower, is around 0.8, so, less than 1 per 100,000. When we look at sarcoma and we start questioning ourselves about is there any difference between males and females, it seems that females have slightly higher incidence, but of course, we need to look at the different sites that are included, because again, here, now I'm talking about soft tissue sarcoma. The way we proceed in this paper is exactly as that was done by Toro and colleagues, so we identified all the different sarcoma morphologies across the different sites. So, we combined all the different morphologies, and we provide the incidence only by site. And here we can see immediately that, of course, when we are looking at a soft tissue sarcoma in females, there is a quite high number of cases that comes up from the sarcoma of the uterus. That, of course, this is gender specific site, which is not present in the males. So, the sex specific site in males is the paratestis one, which, of course, in terms of sarcomas, had an incidence much lower. So, differences between males and females before thinking about a potential different etiology should be interpreted looking at the case-mix of tumor that contributes to the overall sarcomas. I initiated my presentation stressing how heterogenous sarcomas are and in fact, this is foreseen not only by the different sites from which sarcomas may arise from the different histologies, but also looking at the age-peak of sarcoma. Here, I have highlighted some sarcomas that are typical, for example, of children or of adolescents and young adults. So, we can see that in the big group of sarcomas, of course, we have embryonal rhabdomyosarcoma, which of course has a higher incidence in children compared to adults, although some forms of embryonal sarcomas may of course be

seen also in adults; whereas alveolar and the Ewing family of tumors are more typical of the young adults' type of patient. Same issues with regards to the age specific incidence is important to be stressed for bone sarcoma, where we clearly see a different age-peak that differs for osteosarcomas, which are typical in young adults, 15 to 24-years-old. The same would be for the Ewing family of bone sarcoma, whereas, for example, the chondrogenic sarcoma have the incidence peak in the older age group, 65 onwards. So, this is just to give you an idea about how heterogeneous sarcoma can be, as you know, across the age spectrum. For gastrointestinal stromal tumor, the GIST, I would say that you should ignore what has been published so far by population-based cancer registry because population-based cancer registries do collect only cancers that are malignant, so, the behavior is malignant. If they are benign or uncertain behavior, cancer registries do not collect this tumor. Gastrointestinal stromal tumors, accordingly to previous WHO publication, "Blue Book", used to be considered not only malignant, but also benign and a borderline lesion, and that's why in previous data from population-based cancer registry, a part of GISTs are not included. The situation should improve since the last WHO "Blue Book," the one published last year, identified the GIST as malignant only. And this, of course, should have an impact also on the data that will be provided by population-based cancer registry in future. Anyways, some data are available because some studies try to quantify the incidence of the GIST going back to the pathological report, and currently, the incidence for GIST is considered around 1.5 per 100,000 people. If we try to ask ourself "is the incident different across geographical areas?" Slightly differences can be seen between sarcoma and bone soft tissue, and bone sarcoma across different geographical area. Anyway, major differences seem to exist specially in Eastern European countries. To what extent? Again, this is related to specific risk factors or to a more difficult registration due to the difficult diagnoses and therefore, possible under-registration of sarcoma. This is something, of course, that should be discussed, and therefore, these data should be interpreted with caution. No data on GIST because as I was telling you, these are not reliable. But what is more interesting, of course, is to use these data for understanding which is the survival for soft tissues and bone sarcoma. When we deal with population-based cancer registry, the indicator that is provided is the one of five-years relative survival, which is different from the observed survival to which you might be more used to. The relative survival is a proxy of the cancer specific survival. So, looking at these data, you should really consider that you are looking to the sarcoma specific survival. Here, I'm presenting the data from the EUROCARE-5 study. The period of diagnosis refers to 2000 and 2007. We don't have yet more updated data because this collaborative project requires lots of time for calling and checking the data that the different cancer registries provide. So, the period of diagnosis is 2000 and 2007. The follow-up is 2008. What we see in the figure is that the five-year survival seems to be similar in different areas in Europe, but some differences can be seen looking into, specially, the Eastern European region, which is not something specific for sarcomas. Unfortunately, also for many other types of tumors, rare and common ones, the Eastern European Europe is the area with the lower survival compared to other areas in the country. Something important is also provided in the tables close to the figure. Here, you can see both observed and the relative survival because the relative survival is the cancer specific one. So, it is the net of the comparative cause of death in the general population. It is clearly higher than the observed one, and you can see that the relative survival basically decreases with the increasing age, so, older people have a lower survival. And of interest, males seem to have higher survival than males regardless of the age group. Again, this is not something specific for sarcomas, it's something that has been observed also in other countries and different interpretations have been proposed, including a possible role of hormones, female hormones in explaining the difference between male and female survivals. This, I think, from my perspective, is one of the most interesting results. So, what I'm presenting here is not only one year and five-year survival, but also, the conditional survival. What is the conditional survival? The conditional is the five-year survival conditional on surviving one year. What does it mean in other words? Which is the survival of a patient? Which is the five-year survival of a patient if he managed to survive to the first year okay, of the diagnosis? Why is this important? Because it's basically telling us how much important is the first-year survival, and therefore, all the different treatments that are performed within this one year. What you can see, in fact, in this slide is that the conditional five-year survival is pretty the same across the different

European regions. This basically means that if the patient survived the first year, then its survival, it's similar across country. Why is so important the first year? Because in the first year is when the treatment for localized sarcoma basically happens. So, these data are telling us how much the treatment for localized sarcoma might impact, also on the long-term survival of these patients. This is the same data for bone sarcoma. We see that the differences in survival across European regions and countries are much more heterogenous than what we saw for soft tissue sarcoma, and you can see, again, comparing one year, five-years in the conditional survival, you can see that here, we don't really see a conditional survival seen across the different regions. This probably is related to the fact that for bone sarcoma, also, the multi-systemic, the multi-modal approach is clearly relevant and might be of great impact and can differ across countries. So, we really need to pay attention to the different treatments and there, all the different modalities on soft tissues and bone sarcoma. And this is something that can be extrapolated from these data, although they do not provide directly data on treatment. This is the major point. This is a survival trend. So, we try to see whether the survival for sarcoma is increasing, okay? Here we are looking at possible increased survival between the 1999 to 2007. Unfortunately, we can talk only about a relatively low increase in survival for sarcoma. Why? Because I think that one of the major issues of sarcoma is that so far, I talked about sarcoma, it's a big group of cancers, but you know, you will know better than me that this might be good for a general epidemiological description of these diseases, but behind the soft tissue and the bone sarcoma, there is really a very high heterogeneous group of tumors and also of combination of morphology and topography, which is, of course, a challenge that in the clinical practice you have to face every day, and is a challenge that we need to face when we need to perform studies to better understand and to find possible treatments for sarcomas. Sarcomas are so heterogenous that many of them became rare or ultrarare, and they're also difficult to diagnose. In fact, 35% of the revision of the pathological diagnosis have been performed to have a partial agreement, so, there is a disagreement also among expert pathologists in defining sarcoma. This is basically the reason why I presented my population-based data, talking about sarcomas in general, because we need expertise for making a diagnosis of sarcoma and because population-based cancer registries, I was telling you, are unbiased. Because collect any type of new cancer cases, so, for sarcomas, any type of diagnosis of sarcomas, also, those that are previewed by a pathologist, probably now would have not been resulted in a sarcoma. So, that's the reason why, basically, for population-based data, I suggest always to look at the overall data about sarcomas, soft tissue and bone sarcoma without going into the details of the different morphologies, because there are challenges. If you want to have more information about specific incidence data on soft tissue sarcoma and bone sarcoma, I would refer you to this recently published paper that is coming from the French network, NetSarc, that is basically, a network of expert centers of sarcomas, and that ensure basically a revision of all the pathological diagnosis. So, on the basis of this database, which has been initiated since many years, and since that now they are close to be nationally representative. You can find much more data on a specific sarcoma histotype. The last slides I'd like to share with you, are again to stress how difficult can be to count and to perform studies on sarcoma. And this is an effort that was run by Silvia Stacchiotti in the framework over the global society that is studying sarcomas, because, basically here, the point was really to stress how, among the big groups of sarcomas, most of these sarcomas are represented by ultrarare sarcoma, which, of course, for us was an issue because this makes really difficult to perform studies and for us to count them, of course. So, what we basically showed, and I think it's important to know, is that when we looked at ultrarare sarcoma and also ultrarare bone sarcoma, we basically agreed to define ultrarare those within an incidence lower the 1 per million, and based on this definition, we basically showed that the most common sarcoma, really can be counted into two hands, okay? Whereas, most of the remaining types of sarcomas are ultrarare. These figures are for the soft tissue one. These are for the bones one, the similar issue. Few histotype are not ultrarare. Many histotype are ultrarare sarcoma, and we counted them, so, there are 56 ultrarare types of sarcoma in the soft tissue and 21 types of ultrarare bone sarcoma. And I think this is really the challenge that you will find ahead of us for improving the survival of patients with sarcoma. And I leave you, recommending you to visit the RARECARENet website because, here, we have managed to provide data about incidence, relative survival and prevalence for sarcomas. Again, as I was

telling you, these are population-based data, so, they are provided for soft tissue sarcoma overall and for bone sarcoma overall. And I thank you for your attention.