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e-Session n 572 - 13th May 2021

Innovative therapeutic approaches for rare tumors of the head and neck cancers

Dr Resteghini: Hello, Good evening. This is Dr Carlo Resteghini, I'm an oncologist from the National Cancer Institute of Milan and I'm joined by Dr Vischioni, a radiation oncologist who will discuss with us the innovative therapeutic approaches in rare head and neck cancers. Please, Dr Vischioni.

Dr Vischioni: Thank you, Carlo, for the introduction. Thank you all to be here. So, I am Dr Vischioni. I work at the CNAO, National Institute for Oncological Hadrontherapy. Today, I will talk about particle therapy as innovative therapeutic approach for rare tumors of the head and neck cancer. At my center now, we treat patients with particle. We have both protons and carbon ions beams. In Italy, there is only one center like ours. In Europe, there are actually two centers, one in Germany and another one that started clinical activity last year, in Austria. Then, there are two centers in China and five centers in Japan. Here, we refer to a rare tumor definition according to the RARECARE surveillance project and the European Community definition. Among the broad plethora of rare tumors in the head and neck region, in my presentation, I will only present salivary gland tumors and sinonasal tumors. In the first part of my presentation, I will discuss about salivary gland tumors. First, the role of radiotherapy in locoregional disease. Then, I will briefly present what is particle therapy and the evidence for salivary gland tumors treatment with the carbon ions in Japan and Germany. Then, I will briefly give an overview on carbon ion treatment in recurrent disease. Then, in the second part of the presentation, we'll talk about sinonasal tumors, the management and role of radiotherapy and evidence in particle therapy. Mainstay of treatment for salivary gland cancer, for example, for the adenoid cystic carcinoma is radical surgery followed by post-operative radiotherapy. Post-operative radiotherapy in retrospective series has been shown to have significant impact on local control with rates of 95%, 86%, and 79% local control at 5, 10, and 15 years. However, in some retrospective series, it's reported no impact of post-operative radiotherapy on overall survival and some author postulates no effect on recurrence rate, following a recurrent rate. But instead, delay in recurrence with treatment with possibility of radiotherapy. The common feature of salivary gland cancer cells is radioresistant as shown in many in-vitro studies. This is mainly relevant to be taken into account, especially if we consider unresectable salivary gland cancers, where mainstay of treatment remains radiotherapy. Since the most spread form of radiotherapy is photon radiotherapy, conventional therapy, data are available especially for conventional radiotherapy, in unresectable disease. And nowadays, mainstay of treatment seems to be IMRT, with doses higher than 70 Grays with reported five-year local control of around 50%. Due to the biological properties of particles, which I will talk about very soon, however, for unresectable disease also, every particle or mixed beams, including carbon ion has been highly recommended for unresectable salivary gland cancers. The first experience with particle therapy in salivary gland tumors dates back to the 80s of last century, when many publications, as you see in the tables in this slide, reported an overall local control advantage of patients after treatment with

neutron therapy compared to treatment with photon radiotherapy. This, unfortunately, the only phase III randomized trial started based on these data was comparing neutron therapy with photon radiotherapy was closed prematurely due to excessive toxicity of the neutron arms compared to the photon arms only after two years despite the very good local control results on neutron treatment of approximately 70% of the two years compare to the photon arm, where the local control was lower than 20%. So, after this experience, neutron therapy treatment for salivary gland cancer basically was abandoned all over the world. And especially in Japan, the Japanese colleagues started clinical experience with the carbon ion, which is another particle with the same favorable biological properties on effectiveness as for neutron but much better dosimetric profile compared to neutrons. Now, I will briefly talk about the physical and biological property of particle therapy. So, particle therapy is a type of radiotherapy that employs instead of x-ray and photons of conventional radiotherapy, hadrons, which are atomic nuclei. They are drawn here on the slide, on the right-side, from the heavier neon and carbon to the lighter simpler proton. So, proton is a very simple particle whereas carbon ion is heavier 12 times more compared to protons. Both the particle, protons and carbon ion, share a very good dosimetric profile. Since, differently from photon beam, when we use them to irradiate a deep volume in the body, they deliver no dose in the entrance path of the beam, and no dose beyond it. So, the dose is delivered to the target with very high conformality. This can be seen also in this panel here where we have comparative treatment plans of tumor irradiation of the parotid target in the homolateral neck. Comparing photons on the left side and then protons and carbon ions. You see on the CT slice on the left side, all blue color, which is the excessive dose that conventional photon radiotherapy delivered to the normal tissue surrounding the target. And this excessive dose cannot be seen in comparative plans made with protons or carbon ion, meaning that what we were saying before, that then the physical properties of particles translate in very high conformality on the tumor target. This, of course, is also a translation into the clinic. This is something that is being also evaluated in trials. So, this is, for example, a retrospective study on patients treated with photon radiotherapy compared to patients treated with conventional radiotherapy and the patients treated with protons had lower acute toxicity, in terms of dermatitis, mucositis, dysgeusia, and fatigue compared to photon radiotherapy. Besides the physical properties that we were talking about that have in common both protons and carbon ions, carbon ions, and only carbon ions, have specific biological properties that render them more effective on cancer cells, compared to both, protons and photons, three times more effective. This is due to the precise delivery of the dose of the carbon beams at the level of the DNA double helix which causes direct damage to the double helix DNA that cannot be repaired by the DNA damage repair cell machinery and thus, leads to cell fate and cell death. So, this damage caused by carbon ion is also not dependent on cell cycle phase, therefore, carbon ions are also considered to be highly effective on radioresistant clones and furthermore, in in-vitro experiment, has been shown to be potently effective also on cancer stem cells. So, due to all these biological properties I've talked to you about concerning the effectiveness of carbon ion, the Japanese colleagues started treating patients with radioresistant tumors with carbon ions instead of using neutrons which were with very bad dosimetric profile and therefore, had very high-toxicity. So, first results with carbon ion are shown here in this series, published in 2011 from the Japanese group of NIRS in Chiba. Here, they show very good local control, 5ive-year local control especially for salivary gland tumor, over 70%, and very good also overall survival approximately of 70%. Here in the table, you see how these data from the Japanese of NIRS, highlighted in red, can compare to the other published series about treatment of adenoid cystic carcinoma with other form of therapies. So, in yellow, you can see results within surgical series, which well-compare to the results in carbon ion therapy which are only for unresectable tumors, for bad prognosis tumor. Then, also, the Japanese results are much better compared to the photon only results, highlighted in gray in the table. So, but however, there are more series, retrospective series. So, we have a huge lack of evidence for the advantage of carbon ion in radioresistant tumors. Since a few years ago, actually, when the Japanese facilities in operation made sort of consortium in order to analyze retrospectively all the treatment with carbon ion in radioresistant tumors of the head and neck done from 2003 up to 2014 in order to show the efficacy and safety of carbon ion in patients with head and neck tumors except sarcoma. This, at the end, the analysis, the multicenter retrospective trial included

908 patients. All unresected patients, or patients unfit for surgery. So, high stages, mainly stage 3, stage 4, all treated with radical intent. And basically, with no positive lymph nodes. Here in the slides, you can see the mainly publication done on subgroups of this big patient series for sub-studies done for peculiar histologies or subsites. For example, in locally advanced sinonasal malignant tumors enrolled, more than 400 patients, two-year local control, was nearly 80%. Then, for major salivary gland carcinoma, the sub-analysis showed in 69 patients, three-year local control of 81%. Here, you see a detail on the analysis from the J-CROS retrospective multicenter study on adenoid cystic carcinoma-only patients, 289 patients, majority of which localized in the sinonasal cavity, majority T4 tumor stage, with five-year local control of 74% and five-year overall survival of 68%. Late toxicity was also acceptable in these patients, with two patients with toxic death and 14 patients with G4 toxicity, mainly visual loss and brain damage. In this slide, you see then the Japanese data on parotid tumors only, treated with carbon ion. Also, these tumors, mainly unresected or after local recurrence after surgery. Again, with a median follow-up of 62 months, local control at five years was higher than 70%. Overall survival was also nearly 70%. But the most important interesting thing is that 83% of these patients could maintain function after carbon ion. And this is important because when we have a patient that is deemed unresectable, then, we have an alternative, we can offer to patient instead of surgery that will for sure lead to facial nerve toxicity, also, without being effective because will leave for sure R2 tumor persistence. So far, we have presented the experience on carbon ion of the Japanese colleagues. The other big center which has a long-lasting experience on carbon ion is the Center of Heidelberg in Europe, in Germany. In Heidelberg, adenoid cystic carcinomas are treated with carbon ion with a different protocol compared to their colleagues in Japan. In Japan, all the treatment is done with high doses of carbon ion, radical treatment. In Heidelberg, they use a mixed beam approach. So, they reserve the carbon ion boost only for the first part of treatment. And then, the two third of remaining treatment is done with photons, photon beam conventional radiotherapy, on the tumor mass and on the neck. Here, I reported the first trial showing results of treatment of patients with adenoid cystic carcinoma with carbon ion beam, mixed beam radiotherapy. So, this is not a randomized trial. However, is a prospective trial where the colleagues consecutively enrolled the patients for conventional radiotherapy or mixed beam treatment, which means photon with carbon ion. They were all patients unresected or R2 patient and, as you can see here, the results of outcome for local control progression-free survival and overall survival was much better in the mixed beam arm compared to the photon arm. At the moment, the German colleagues are even treating patients with carbon boost at higher doses in order to try to overcome radio-resistance of this tumor type. And they have even better results than this. Most interesting in their study was that our colleagues did not see any difference in local control in their series between R2 resected patients and unresected patients which was also confirmed in following publication from the same group also in bigger series of patients, which underlie that in case of very huge disease, default tumors, debulking surgery or demolitive surgery is not necessary. And carbon ion can be discussed with the patient, the use of carbon ion as a radical treatment in alternative. Of course, more publications came out also from the center in Germany on the use of mixed beam treatment, photon plus carbon ion in different locations of adenoid cystic carcinoma in the head and neck. Here for example, I reported the experience in oral cavity tumor. In this case, carbon ion boost was used mainly in post-operative setting after surgery with marginal residual. Due to the biological properties of carbon ion, which I mentioned before, carbon ion can even offer to patients in case of relapse after a multiple treatment and a previous radiotherapy course as re-irradiation. Here, I report the experience from our center, now, in Italy, where in a series of 51 patients, where patients were enrolled for re-irradiation with carbon ion, and the dose is from 50 up to 60 Gray equivalent with an advantage in overall survival in the series of 63% after two years and in progression-free survival, 52% after two years. Now, we move to the second part of my presentation, which will be on sinonasal tumors. First, I will present the management and role of radiotherapy in locoregional disease and then, evidence in particle therapy. So, sinonasal tumors are usually managed with surgery. Radiotherapy is also used in post-operative setting with schemes and results depending on stage, histology, margin, status, and grading. New high precision radiotherapy techniques has been reported to improve local control in patients with this specific tumor locations. In case of locally

advanced sinonasal tumors, radical radiotherapy treatment can be offered in unresectable patients with addition of chemotherapy. There are reports showing an improvement in prognosis in histology-driven chemotherapy and neoadjuvant chemotherapy. Furthermore, in some series, has been shown the advantage of multi-modality treatment including chemotherapy, radiotherapy, and surgery over single modality treatment or dual modality treatment. So, sinonasal tumors include a high variety of histologic types of tumors. Some of them are listed here from the more radiosensitive one, the squamous cell carcinoma and undifferentiated carcinoma, to the less radiosensitive, adenoid cystic carcinoma which we talked a lot about before and also mucosal melanoma. So, the use of particle has been advocated for sinonasal tumors, both with protons and carbon ion. Protons had been advocated especially for radiosensitive histologies in order to spare toxicity and escalate the dose to the target in this very delicate region, in the middle of the base of skull, where we have eyes in one side and we have the brain, then, we have the optic nerves and so on, very delicate structures that we want to preserve with the use of protons and with a dose conformality of treatment planning done with protons. Then, carbon ions can be used to increase effectiveness and cure rate on those very radioresistant histologic types such as salivary gland tumors, or mucosal melanoma tumors, or very poorly differentiated tumors. So, which are the evidence for the use of particle therapy in sinonasal tumors? I like very much this meta-analysis that was published in 2014. At the end, 43 publications were considered, 13 with particle and 30 with photon. More than a thousand patients were included in the analysis. And the authors managed to show five-year overall survival advantage and disease-free survival advantage, locoregional control advantage, for particle therapy compared to photon therapy in sinonasal tumors. Of course, authors also highlight also the bias of this type of study. This is a study that includes series of patients treated with different modalities, not only with photons but also different modalities of particle therapy. So, they include carbon ion, mixed beam therapy, particle therapy. So, very different types of treatment and also, different types of patients included in the analysis. Furthermore, the meta-analysis focuses on toxicity and what they see is a higher toxicity of particle therapy compared to photon therapy, higher neurological toxicity. They suggested the explanation for this. Particle therapy studies are usually more detailed than toxicity compared to photon studies, because this is an emerging technology so, we want more data about the conformality of this type of treatment, that more challenging cases are sent to particle therapy instead of photons. And then, with particle therapy, it is possible to deliver higher doses compared to photon radiotherapies. So, at the end, to draw a conclusion about the effectiveness and safety of particle therapy, we need registers for comparison or a randomized trial. This is a table from a review from the group of Gustave Roussy, in France, where are summarized data on proton therapy in sinonasal tumors, in series not included in the meta-analysis. In these series, all they show that treatment with the protons gives an improvement of local control compared to the historical cohort with the photon. But only one of them managed to show, the McDonald one, managed to show a toxicity advantage of the proton therapy compared to photon therapy. This is another meta-analysis, this time done on all head and neck region not only in paranasal sinus, including 74 conventional radiotherapy studies and 12 particle therapy studies. Here, the authors showed five-year better local control for paranasal sinus treated with protons versus treatment with the conventional radiotherapy. And five-year overall survival improvement for mucosal melanoma treated with carbon ion compared to treatment with intensity-modulated radiotherapy. Also, in this case, the author concluded that these are results that need to be confirmed in larger randomized trials or international patients' registry since the carbon ion facilities, particle therapy facilities are so little in the world. So, we need to gather more data and gathering also forces with different radio-particle therapy centers. These are Japanese data about treatment with the carbon ion on mucosal melanoma. This, again, come from the J-CROS trial I talked to you about before. Out of 260 patients with mucosal melanoma, majority of which are the sinonasal cavity, as you see, local control was very good and same for overall survival. In this table, I compare the data on overall survival of the Japanese trial with the carbon ion to what is published in the literature on overall survival in treatment with surgery and the X-ray for these tumor types. And you see that compared to conventional treatment, carbon ion had a very huge advantage both on three-year and five-year overall survival. So, to conclude, we have shown that carbon ion can improve local control

especially in non-radiosensitive tumors such as salivary gland tumors and malignant melanoma. Proton therapy has the potential to improve local control in dose escalation studies with acceptable side effects. No guidelines are available to help clinician in the choice between photon radiotherapy and particle therapy, this is true especially for protons. For non-radioresistant tumors in the sinonasal cavities, such as squamous cell carcinoma, sinonasal undifferentiated carcinoma, and neuroendocrine sinonasal carcinoma, we can propose a model-based approach to implement how to address patients to treatment with proton versus treatment with conventional radiotherapy based on the advantage on toxicity that we can have with proton versus conventional radiotherapy. Finally, as also stated in the two meta-analyses I have shown you, large prospective studies or international registry search should be designed to face the efficacy and toxicity clinical issues for particle therapy, both protons and carbon ion. Thank you, I'm finished.

Dr Resteghini: Thank you, Barbara. And it's a very great overview on the potential of those techniques. First of all, as this slide remember us, I will like all the participant to ask any questions they feel they have on these topics. We want this session to be as interactive as possible. In order to break ice, I think I'm going to start with some comments. And the first one is that we discussed a lot about radiotherapy over this session, but you mentioned several times the necessity to integrate this methodology with all the other weapons that we have. So, I would like first of all, to stress and highlight the need for multidisciplinary management of these rare diseases. And speaking of rare, we are discussing salivary gland tumor, we are discussing sinonasal malignancy. Those are very rare tumors as we saw before. So, my first comment is that the rarity is not just about the type of tumor, but it's also about the facility where we can treat this tumor properly. You show that at the very beginning of your presentation, the scarcity of this type of methodology. Because other than in Japan, you on average, have to travel thousands of kilometers to reach a center like yours. And at the same time, the rarity of diseases, like the one we are discussing, it's for sure recommends the task for a treatment in a reference center with high-volume cases that are able to offer patients with these rare diseases the best treatment options. On the same level, on the same tone, I think that the rarity of those diseases asks for knowledge. We assess those tumors, are rare, we need to create knowledge. And how do you create knowledge on something that is rare? You collect data, as you said, in your last point for the take-home message, we need registry and we need to collect data on this type of treatment, this type of tumor, and this is one point. But at the same time, I think the real challenge is to produce some study of all of the important data you presented. Very few were derived from prospective study. If I remember correctly, maybe just one, the one from the 80s. I was born in the 80s, so, it's quite some time. We miss some prospective data in this type of tumors. And speaking of studies, speaking of generating prospective data, prospective studies on this rare malignancy, I want to start the discussion with you discussing about introducing how are common experience for all of the people connected and who will listen into this presentation and record the presentation, I wanna point out that my institute is quite close geographically to the CNAO center, in Pavia, and we are collaborating on a regular basis since quite some times. And for example, we have run recently a couple of prospective clinical trials on sinonasal malignancy called SINTART study. The results are very mature right now and we're going to present part of the results in the upcoming ESCO meeting and in the ESMO meeting as well. And those studies, those prospective studies, evaluated the combination of a multi-modality treatment with induction chemotherapy surgery for resectable patients and radiotherapy, both with photon and with particles, and the combination of those treatments were based on several factors, especially, on the type of response to induction chemotherapy. So, to start with some questions, since nobody from the audience, I see, has already broke the ice, and I invite you again to ask some questions. Feel free to ask whatever you feel like, there are no stupid questions. Speaking of how our experience in the SINTART studies, I don't know but if you wanna comment on the difficulties, the challenge that we encountered, speaking of integration of different treatments and the challenge especially for maybe those patients with important tumor shrinkage, important response with shift in the brain due to the tumor reduction or the generation of a bunch of air space, aerated space, close to the target due to the tumor shrinkage. And what were the challenges that you encountered in your experience?

Dr Vischioni: Thank you, Carlo, for your comments. I think you touched very important points, absolutely. So, we are the only center in Italy treating with particles and we mainly treat rare tumors because actually indication for particles it's basically rare tumors. So, now, I might say, that we have quite an experience with that treatment of salivary gland tumors and treatment of sinonasal tumors, and sometimes, salivary glands in the sinonasal. But so, it is very, very important collaboration with the referral centers where there is a very high expertise in these malignancies and rare tumors, such as the center where you, Carlo, work, because we need to have a pathologic evaluation of the samples just to... because we do then histology-driven chemotherapy. So, we need to know precisely what is the tumor. Then, we want to give the best chemotherapy to the patients. And afterwards, if the patient responds to chemo, and I'm talking about this SINTART experience, then, they can undergo the best surgery for their tumor. So, let's say that the management is very complex and in very close collaboration with referral centers of the patients and with the centers where the patients do chemotherapy, surgery, and then, also, all the imaging and the analyses that we need then to address the correct treatment, even with particle for these patients. Then, not last to mention, then, also, in the case of our patients, we do a patient-tailored radiotherapy, because even for us, in case of radioresistant histology, we can deliver radical treatment with carbon ion, or in case of more radiosensitive histologies that respond well to chemotherapy, we can offer mixed beam of photo-radiotherapy together with particle radiotherapy. And of course, then, we need very close collaboration with the other radiotherapy centers, because there is a lot of work on any of these patients because we need to exchange images, exchange treatment plans, information about the patient then, coordinate very well the appointments of the patient in one center and the other one. So...

Dr Resteghini: So, logistic is also involved. I have a question from the audience, they asked about if there is any difference in the radiosensitivity profile of different subtypes of salivary gland tumors; we discussed mainly about adenoid cystic carcinoma. Here, I have a question. If in your experience, there is a difference between the radiosensitivity of hormone receptor-expressing tumors or tumor with no expression in hormone receptor?

Dr Vischioni: Let's say that there are no well-designed preclinical studies about this very important issue, mainly because if we are talking about carbon ion, even the carbon ion beam is a kind of rarity, carbon ion beam for preclinical experiments. So, it's also difficult to address these questions. But according to my experience, with, of course, patients with adenoid cystic carcinoma, solid variants which are known to be more aggressive tumors are the more radioresistant, meaning that we see also in a preliminary analysis, and also, has been shown by the Japanese colleague in a publication of two years ago, the correlation between local control for adenoid cystic carcinoma and the different histologic types, of course, being the solid variant, the most radioresistant compared to the other histologic types. Regarding the expression of, I must say, then that, maybe, you have a bit more data about that because of sometimes we refer relapsing patients to the oncologist, to your center. And then, when we do histologic revision if we find positivity for receptors then, they can undergo treatment regarding the progesterone receptor.

Dr Resteghini: Exactly.

Dr Vischioni: And what we ... still we do not have enough data, but it seems that previous treatment with carbon ion managed to prolong survival of these patients or gives better results to following systemic treatments. Of course, the mechanism of this is still being investigated. It is known that carbon ion is highly immunogenic. So, it might be that immunologic response is involved in a kind of immunotherapy-like way.

Dr Resteghini: And speaking of that, if I may interrupt you, is there any possibility of integration of the different immuno-therapeutic agents that have taken the main stage in oncology? So, like, involve Pembrolizu. and other agents commonly used in everyday oncology? Is there a path for integration of these new drugs with this innovative type of radiotherapy? Because as you mentioned before, this is a quite powerful tool. To me it's quite toxic tool if we mix it with chemotherapy. And so, we lack data on the

combination, we lack a lot of data on the combination of particles, radiotherapy and chemotherapy, but is there any data at all on the combination of immunotherapy and particle radiotherapy?

Dr Vischioni: So, as you know, as primary treatment, we never combine carbon ion for head and neck, with chemo or systemic therapy or immunotherapy because of risk of toxicity. We do not dare to do it, I mean, in patients at first diagnosis. So, for other tumor sites, there are combinations of chemo and carbon ion, but of course, head and neck is a different site.

Dr Resteghini: Quite unique setting.

Dr Vischioni: Exactly, exactly. And so, but we hope, in the future, to show or wait, for the moment we do treatment with carbon ion, then, we have a washout of 10 days, and then, we start with chemotherapy, kind of same thing we do for in treatment of mucosal melanoma in combination with immunotherapy. So, as a radical treatment, first treatment, we never associated the...

Dr Resteghini: Two treatments together. Okay. I think our time is over. I do not see any other questions. I don't know if, Barbara, you wanna make some final remarks or?

Dr Vischioni: So, I thank you, Carlo and everyone for joining the session. I hope also, we want also to receive patients for treatment. So, because we treat rare tumors, therefore, if you have patients, we referred over these tumors types we have talked about, we are happy to discuss about that and address them to the right treatment or offer also this opportunity. For the rest, as for the issue of systemic therapy, we need more data. I think it's an open field to investigate. So, I think it should be done starting from maybe relapse patients, metastatic patients, just for to investigate the role, the addition of systemic therapy to carbon treatment and moderate the doors, maybe, for this type of combination treatment, an interesting field.

Dr Resteghini: Okay. So, thank you, Barbara, for your presentation and thank you all for your attendance. See you next time.

Dr Vischioni: Thank you.