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Particle therapy in the treatment of GI cancers

Dr Vitolo: Good afternoon. My name is Viviana Vitolo. I'm a Radiation Oncologist, and I work at the National Center for Oncological Hadrontherapy, in Italy. This evening, I would like to discuss with you and to give you a brief overview about the role of Particle Therapy in the gastrointestinal cancer, and my attention will be focalized on pancreatic cancer and locally recurrent rectal cancer. So, let's start with a short introduction about a Particle Therapy and the advantages compared to conventional radiation therapy. First of all, Particle Therapy is characterized by its physical selectivity. So, particles have the opportunity, the possibility to deliver the dose in a specific region in the tissue while sparing the surrounding organs at risk, and this is typical for protons and carbon ions. From the radiobiological point of view, carbon ion is considered much more effective than protons and photons, and the RBE is up to 3 times higher than proton therapy. The big mass, the charge of the particle allows these two carbon ions to give a damage to the tumoral cells' DNA and to create double-strand breaks in the DNA. So, the damages on the tumoral cells are difficult to repair. Okay, so, I start to discuss about pancreatic cancer now. We know that pancreatic cancer is a very aggressive disease, is known as a big killer, and to date surgery is the only potentially curative treatment for this disease. Pancreatic cancer has a very poor prognosis, and 5-year overall survival is very low. Of course, prognosis is related to the extension of the disease, and when cases are resectable, of course, overall survival is better than in unresectable cases. Literature reminds us that surgery and chemotherapy both can increase local-control rate and survival for patients. Concerning conventional chemo-radiation therapy, if they can improve, improve local-control, it's questionable then its role about survival. In particular, these randomized controlled trials show that with the conventional radiation therapy-dose with X-rays, there is no, in association with chemotherapy, there is no-benefit compared to chemotherapy alone, in the overall survival of patients with locally advanced pancreatic cancer. So, pancreatic cancer is the typical radioresistant tumor, and from the radiation oncologist point of view, the only way, a possible way to increase the result of such a treatment is to increase the dose, to escalate the dose. And these articles show how increasing the dose, for instance, to more than 61 Gy with the simultaneous integrated boost is possible to achieve better significant overall survival than with the lower doses, and the overall survival is described up to 21 months. And so, stereotactic radiation therapy with photons is now considered the most commonly used treatment modality to treat pancreatic cancer. This systematic review, analyzing 19 trials about stereotactic radiation therapy, shows that the median-overall survival with such technique is around 17 months with a local control-rate of 70% and 1-year overall survival of 50%. Most of the articles analyzed in this review do not show results about the 2-year overall survival. The other important aspect is that with the stereotactic radiation therapy, which is feasible, severe adverse-event do not exceed 10%, but the other conclusion of this study is that is necessary a definite validation of this treatment with large randomized trials, because in the analyses, if you see there are no phase III trials describing or highlighting the superiority of this technique, compared to others. Another

important aspect from the radiation oncologist point of view is the definition of target volume. In stereotactic radiation therapy, the target volume is defined by the gross tumor volume plus a margin of 3 to 5-millimeter, keeping into account the setup organs and movements of the target. We have to remind that pancreatic cancer, as all the abdominal targets, isn't moving far. It's important that with this small target volume, and with this so conformal technique there is a high-risk of local failure. And this article, describing the experience on 500 patients treated with the Cyberknife, for locally-advanced or inoperable disease, show a very high rate of local failure, especially, out-of-field or at the margin of the field, stressing the concept that high conformality is advantageous in terms of dose-escalation, but on the other side, it's risky for local-recurrence. So, it's necessary to enlarge the target volume to avoid such recurrences and the authors say that, of course, it's important to treat very well the region of the splenic vessels and this can impact not too much on the possible gastroenteric toxicity. Okay, let's go to the Particle Therapy. As for stereotactic radiation therapy, even for Particle Therapy, there are no randomized controlled trials and most of the data are retrospective and from mono-institutional experience. And most of the experience comes from Japan. Here, a retrospective analysis of Proton Therapy concomitant to chemo. therapy for 42 patients with locally advanced disease. These patients were treated with dose from 50 to 67.5 Gy, depending on the location of the tumor, and the authors found very excellent results because the median overall survival for patients was 25-months, which is much higher than the reported results in the literature for photons and 2-years, and overall survival was almost 50%. Farther, they did not report any grade-3 toxicity or other adverse-events. And now, the experience about carbon ion radiation therapy, which comes from Japan, again, and from the National Institute of Radiological Science in Chiba, Tokyo. We can consider this Institution the pioneer of carbon ion radiation therapy. They defined, they have 20 years of experience, and they were able to define the dose to use in the clinical practice. So, they started with dose-escalation studies and, for pancreas, started with carbon ion radiation therapy alone, first. Then, in a second step, they associated the gemcitabine, concurrent gemcitabine for treatment, and now, in the clinical practice they have defined what is the, let's say, right dose to prescribe for patients. Shinoto, in 2016, described their activity in dose-escalation studies for locally advanced pancreatic cancer, showing how starting from 43 Gy to 55.2, they increase, at the same time, the dose of gemcitabine, defining the right and the correct dose of prescription to 1000-milligram of gemcitabine concomitant to this 55.2. He, also, shows in his article how a higher-dose, they could achieve a better overall survival up to 24 months and 2-year overall survival of about 48. Grade-3 gastrointestinal toxicity was only 1% in this experience, but this was just a mono-institutional experience. In another article, Japanese show how these mono-institutional results were really confirmed by different others experiences. So, in the JCROS, which is the Japanese carbon ion oncology study-group, they decided to put altogether the experience of three different centers using carbon ion radiation therapy and found, actually, the same results. So, again, with doses between 52 and 55 Gy they obtained a median survival time of 26 months for the higher-doses and a general overall survival of 21.5 months. We were discussing about the target volume for stereotactic. In carbon ion radiation therapy, target volumes are bigger. So, Japanese include not only the tumor, the macroscopic tumor in the target volume, but a margin including regional lymph nodes. So, bigger volume to avoid local recurrence. Carbon ion radiation therapy in pancreatic cancer is for sure, a very complex treatment and critical because, as everyone knows, pancreas is in the middle of the abdomen and the organs at risk, if pancreatic cancer is a very radioresistant tumor, on the other side, the bowel loops are very, radio- sensitive. So, it's necessary to minimize the movement of the target and of the organs around the target, and to do this, it's necessary to make compression of the abdomen to realize 4D CT scan. So, the delivery of the beam has to be synchronized with the breathing of the patient, and so, it's necessary what is called the Respiratory Gating, and then, it's necessary to re-plan very often the treatment to verify if really the planned-dose is delivered in the right place. The experience of Japanese also includes the pre-operative, neoadjuvant treatment for pancreatic cancer. So, Shinoto, again, defined a study, a phase I study, escalating the dose and before surgery. So, they analyzed 26 patients, and 21 of them were resected. And they obtained a 0 rate in 19 of them. In these patients the overall survival at 5-years after surgery was around 50%, and the data, updated data about neoadjuvant treatment show even better result in terms of overall survival for such

operated patients, even better with higher-dose up to 62%. Based on the background from Japanese, at our Institution we defined a protocol similar to what was defined by the Japanese, and now, we have this PIOPPO trial with enrolling patients for preoperative chemo-radiation therapy for borderline resectable pancreatic cancer. The scheme is quite similar. So, after staging and three cycles of Folfirinox patients go to radiation therapy and receive 8 fractions, 4 fractions a week of carbon ion radiation therapy up to 38.4 Gy, and after 4 to 6-weeks, receive surgery. The aim of the study is to see if it's possible to recreate, to obtain the same results from Japanese and to investigate the local progression-free survival, the overall survival, the resectability-rate of such patients, treatment toxicity, and perioperative toxicity. So, to conclude about pancreatic adenocarcinoma, we have seen that carbon ion radiation therapy in locally-advanced disease and in borderline resectable disease can increase overall survival. Of course, it's necessary to investigate more and maybe possibly to have randomized trials to make this contribution. The other topic I want to discuss with you is the management of another challenging situation, which is the recurrence from rectal cancer. Locally recurrent rectal cancer is defined as an isolated pelvic recurrence of disease. The incidence is about 4 to 15%. And again, salvage surgery is the mainstay of treatment, but it's not possible all the time. And debulking surgery is not recommended by guidelines. So, as alternative to surgery, radiation therapy it's a possibility, but conventional radiation therapy is limited by the radiation therapies already performed for these patients, who receive, generally, preoperative radiation therapy and a more selective technique might be a possible alternative. The reasons are the same than pancreatic cancer, even recurrent rectal cancers are radioresistant tumors. And so, a more selective technique and a biologically more effective technique might be a possibility. About the experience, again from Japan, this study from GUNMA University evaluates 28 patients treated prospectively with very high-dose, 73.6 Gy in 16 fractions. Most of these patients, actually, did not receive a preoperative radiation therapy, and this is the reason of such high-doses. But local control-rate and overall survival are excellent, and even toxicity is very low. And Shinoto, then from Chiba center, describes another retrospective analysis on 200 patients, and what is interesting is the inclusion criteria. It's important. It's important in case of re-irradiation of the pelvic region that the lesion presents a certain distance from the digestive tract and the bladder and no active infection has to be present. Even the Chiba center prescribed very high-doses, 70 or 73.6 Gy. And again, most institutional studies show a local control rate up to 88% at 5-years and a good overall survival rate with mild toxicity. Just one case of a gastrointestinal reaction and two infections and a neuropathy as late toxicity. Re-irradiation by carbon ion was also presented by the German colleagues from the Heidelberg center, but in a smaller casuistic, of course, they described patients already treated by radiation therapy. And so, this is more common in our countries, and do not allow so high-dose as described by the Japanese. So, generally, after previous radiation therapy, it's possible to deliver doses based on the analysis of the previous VDH and of the previous plan. So, a range of doses is possible up to the tolerance of the organs at risk. Anyway, even German colleagues do not report a higher toxicity and had a quite good local control, but they do not find a predictive value in terms of dimension of the tumor treated and dose delivered. Even our center experienced and published data about re-irradiation for rectal cancer disease. It's more serious, 14 patients. Again, a range of dose depending on the previous radiation therapy delivered, but interesting results in terms of low side effects and quite good local control. 2-years overall control was around 52%. The necessity, the need of distance between the tumor volume and the gastrointestinal loops is evident even in our experience, and in case it was not possible, we had the opportunity to use a spacer implantation to make, to create this distance. Now, to conclude, carbon ion radiation therapy is possible, is indicated when there is such distance we were discussing about or, if not present anatomically, this can be created by a spacer positioning. Of course, it's necessary to know very well the details about the previous radiation therapy to deliver as much dose as possible in the new treatment, and carbon ion can be a solution because of its radiobiological effectiveness, may be feasible and may be advantageous even in locally recurrent rectal cancer.

Dr Cobianchi: Thank you, Viviana. Thank you for your presentation. Good evening, everyone. At the moment, we do not have any questions from the audience. So, I do not have specific questions, but let me tell you that

I believe that for the pancreatic area the neoadjuvant therapy will be the future in the treatment of pancreatic ductal carcinoma, probably, also when the tumor is primary resectable. So, the integrated approach is, in this type of cancer, the key-point for what certainly it represents an unmet-medical need. I would say that we do have experience in surgical treatment after carbon ion therapy here, in Pavia, and what we can say from a surgical standpoint is that the surgical field is quite fibrotic after carbon ion therapy. And so, we have some problems. It is a little bit tricky, the removal-time for the cancer, but the reconstruction is easier, due to the pancreatic remnant that results, fibrotic and so, generally speaking, favorable for the pancreatic jejunal anastomosis. So, in summary, I think that integrated approach is the key-point, and so, you underlined this point very well, in your presentation, Viviana.

Dr Vitolo: Okay, and from the Radiation Oncologist's point of view, especially, concerning the pre-operative approach is complex, as we have discussed but it's well-tolerated by patients because for such doses, actually, they do not complain any particular problems during treatment. Of course, it's complex. They need to perform a CT scan weekly. We have to recalculate all the dose. They have to perform several CT scans before treatment, because we have to exactly know where the bowel displaces all the time. And the impression right now is positive.

Dr Cobianchi: Okay. Thank you, Viviana. We do not have any questions from the audience. So, I think that your presentation was very clear. So, I don't know, we can...

Dr Vitolo: Maybe, if we have to continue a little bit before closing, maybe, you can tell us something about the place, the spacer displacement. We have this nice collaboration with you and for recurrent rectal cancer and for sacral chordomas, which is not the topic of this presentation, you are helping us in treating a very complex disease with a very high-dose, in case, for instance, of sacral chordoma, helping us with the spacer positioning. So, if you want to tell us something.

Dr Cobianchi: Yes, yes, yes. We have experience in surgical spacer placement before carbon ion radiation therapy for sacral chordoma, for rectal cancer. So, the point is we have to put a space between the tumor and some structures that are particularly sensitive to the carbon ion therapy. We have used silicone and we used also epiploon, so, the fat that is in the abdomen. For both the conditions, we had good results, and so, this is another instance of integrated approach, in this case, surgical approach before carbon ion therapy and then, an optimization of the carbon ion therapy after the surgical treatment. So, this is another interesting application of surgery in radiation therapy.

Dr Vitolo: This is a very nice multidisciplinary approach to the patient. All the time is a question, a discussion about multidisciplinarity in the treatment, in the management of patients, and we are, for sure, an example of this. So, I thank you for this opportunity and this collaboration.

Dr Cobianchi: So, thank you, Viviana.

Dr Vitolo: And Thank you, Lorenzo.

Dr Cobianchi: Thank you for your attention, and have a good evening.

Dr Vitolo: Thank you. Thank you to all the participating people, and have a good night.