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Next-generation hadron-therapy: Next Ion Medical Machine Study

Dr Vretenar: Thank you very much. I will start sharing my screen. Perfect, okay. So, good evening, good afternoon, and good morning, depending on where you are. I have to thank the ESO for giving me the opportunity of making this lecture and of presenting our work. I'm really excited at the idea of addressing your community because I am really a hard physicist. I've been working more than 30 years designing and building particle accelerators. And only the last five years of my career, I've approached the fascinating world that is between physics, biology and medicine, because I'm convinced that in science now every big progress can come only at the boundary between disciplines. So, I will present to you my work in exploring these boundaries, and I'm really looking forward to your questions at the end of my presentation. All right, so first of all, as you might know, I work at CERN. What is CERN? CERN is a large international organisation and is the largest laboratory in the world for particle physics. CERN stands for Conseil Européen pour la Recherche Nucléaire. It was founded in 1954 to promote science for peace, and nowadays we have 23 member states, 2.500 employees, 10.000 users coming to our installations. So, it's a large structure and our mission is science. Science, but also technology, also training of the young generations, and establishing collaborations. We want to be a meeting-point for particle physics and for science at the European and world level. And what can we do for medicine? So, maybe you know that we are operating the largest complex of particle accelerators in the world. So, our flagship is the Large Hadron Collider, 27 kilometres of superconductive magnets. And to build and to operate this accelerator, we had to develop a lot of technologies that might have applications on society. And we are engaged to trying to exploit these technologies and to bring them to society. We aim to show that there is a return from basic science towards society, and that what we do is also an application in other fields. And medicine is the main field of application that we have found for our technologies. Okay, take the pointer, all right. And this thanks to the fact that particular accelerators can give access to the subatomic world. So, this is what we can... we can use our beams to really access to the atoms, to the components of the atoms, and try to see how we can use their properties in medicine. And we are also a good place for creating the collaborations that are needed to push forward these technologies. But now, let's come to the subject. Yes, to the subject of today's lecture: treating cancer with particle beams. So, you know very well that X-rays that were discovered in 1895 have opened huge perspectives for medicine. X-rays are something very simple. We physicists, we call them photons, because actually they are tiny particles that don't even have a mass. And with them, you can very easily image and treat elements and tissues at the level of molecules and atoms. But if you want to go further to something even smaller, you have to use particular accelerators. Particular accelerators had been invented in 1932 and gives really tools to go beyond the atom and to access to the subatomic components of the atom. Particle accelerators, different from X-rays, accelerate protons and ions, and you see here is one example. So, a protein with a very tiny mass and an ion is basically a nucleus, an atomic nucleus, which is made of protons and neutrons. And here, you have an example of a particle that is used, an ion that is used for medicine. The carbon ion that has six protons and six neutrons. These particles you can use as projectiles. You can create beams of these particles; you can send them against the matter. This might be a block of metal or it might be human tissue. And protons and ions have a very interesting property. They deposit their energy well inside the body at a well-defined distance that is proportional to the energy of the incoming beam. So, different from X-rays that instead give most of their energy at the surface, and then you have less and less energy inside the body. Protons and carbon ions have a precise peak that is called the Bragg Peak and gives us an incredible opportunity of using it in medicine. It really corresponds to the ancient dream of bloodless surgery, of being able to intervene to the possibility, therefore, to destroy cells without damaging the skin and the tissues before the place where you want to intervene. So, it is an exciting opportunity, and also this gave birth to the rise of particle therapy. Originally the idea of using particle beams, protons, or ions, usually we call them hadrons. So, sometimes in literature, you will see the word hadron therapy. Hadron therapy using protons and heavier ions. This was first proposed immediately after the War, in 1946. The first hospital that was using proton therapy was doing it from 1993. And for most of the '90s and early 2000s, treatment, in particularly in Europe, with particle beams was done in scientific laboratories for a few patients. But from about 2006, there was a big boom of small proton therapy machines that became commercial. So, nowadays, there are six vendors on the market where you can buy a proton therapy machine, but only one for carbon ions, and you will see that the situation is very different for carbon ions. So, it's a success story, but still there are many discussions. We are not yet fully exploiting the potential of particle therapy, and you will see that there are many ongoing discussions on comparing effectiveness, costs, and benefits of this type of therapy. Because the Bragg Peak in itself is not all. So, the Bragg Peak is something that is a concept it comes directly from physics. And we physicists, we like to think in terms of energy. We want to deposit the energy in some place, but then, what happens with this energy? This is a more complicated story, and in fact is where biology comes in, because the deposition of energy actually transforms into ionisation of the atoms. So, the energy that the particle loses inside the tissue goes to ionising the atoms that break the molecules. So, basically molecule breaking. In some cases, it can kill the cell. In some cases, it can have other effects. So, there are different parameters that come into play. The linear energy transfer that depends on the type of ion, how much energy the ion delivers, and then, the radiobiological effect, which is the effect of this energy in killing the cells. And this is quite complex and requires a lot of experimental work to master the effect. The biological effect of a particular beam requires complex models, and then, when you go to treating patients, very sophisticated treatment plans. And then, we have to consider two other difficult points, two other, let's say, points that we have to consider. First of all, that a tumour, usually, if you want to treat a tumour with these particles, the tumour has a certain depth. So, you have to scan with your beam different depths with different energies, and basically this also leads to an accumulation of the dose in the entrance part. So, at the end, you don't profit completely off your Bragg Peak because of this entrance dose. And on the other hand, the more accurate the tool, the more accurate must be the delivery of this beam. So, we are a very precise tool to attack cancer, but it also requires very accurate imaging before the treatment, compensation for the organs in motion, and this is something where there is still quite a lot of experimental work going on and still there is lot of space for, let's say, for additional progress for fully exploiting the potential of this type of therapy. But I would like now to say something more on ions as compared to the other particles that we can use for treatment. Ions, you see here the carbon ion, are much heavier. They deposit much more energy, so, they have a higher radiological effect, but also, they act in a different way. So, for example, when they cross the DNA, they break the DNA twice. While protons usually create a single breaking of the DNA that is usually easily repairable, ions, and carbon ions in particular, create a double-strand breaking that is not repairable. So, the effect is much stronger for ions, is different from protons or X-rays. With the consequence, the positive consequence that this type of effect is active against hypoxic radioresistant tumours that are resistant to both X-rays and proton beams. So, with ions, you can cure radioresistant tumours, the energy deposition is more precise, and on top of that, there are very interesting work going-on on combining ion therapy with immunotherapy. That could be a way to treat diffused cancers and metastasis. So, a lot of work in this respect, but treatment with ions is relatively recent. The first patients were treated in the early '90s, and the next problem that we have is the size of the accelerator. Because the advantage of ions is that they deliver more energy, but the disadvantage is that you need more energy to enter the body and so, you need a larger accelerator. To give you an idea of how a particle accelerator works, we use a magnetic field to keep the particle in the circular trajectory. And the higher the energy, the larger diameter of our magnetic field. So, producing X-rays for conventional radiotherapy is relatively easy. One can use a small linear accelerator, about 50 square metre, 5 million Euros. To accelerate protons for therapy with protons, it's 10 times larger, more or less the size of the facility, and something less than about, say, 40 million Euros is about the cost of a proton therapy system. But to go to use ions, you need a synchrotron, a different type of accelerator with respect to the cyclotron, and you need to go nowadays to something of the order, to another order of magnitude in terms of size and to a larger factor, in terms of cost. And you see here examples of cyclotrons for proton therapy and synchrotrons for heavy ion therapy. A synchrotron is more or less like a hollow cyclotron. You can think of a synchrotron as a cyclotron where you only use the external part of the machine to create your magnetic field. So, it is much bigger, and it is one of the reasons why we don't have many ion therapy accelerators now in operation in the world. In Europe, we have only four centres that can deliver therapy with carbon ions: two in Germany, Heidelberg, and Marburg; one in Italy, in Pavia; and one in Austria at Wiener Neustadt. And to give you an example of the size of these types of facilities, you can see here, the ion gantry of Heidelberg. This is the system, the rotating system that is used on the Heidelberg machine to position precisely the beam on the patient. You see it's 600 tonnes, and you see here the size of the people here compared to the size of this machine. So, they really are huge beasts. But nowadays, all these machines have been designed in the '90s, so, it was last century, last millennium, even. Now particle accelerator technologies has made a huge progress next to recent achievements, and the question is, could we explore now new accelerator designs where we can profit of the latest advance in accelerator technologies to promote, to push forward, to make more accessible therapy with ion beams? And now, here I make a short break to see if there are questions. I don't know, Luca, if I can continue or there is any...

Dr Bertolaccini: No, you can continue and we could discuss at the end of the presentation. Thank you, Maurizio.

Dr Vretenar: Great, thank you, Luca. So, a strategy for CERN. So, at CERN, we are an international organisation, we don't want to enter in competition with private companies like those that are now producing systems for proton therapy, but instead there is an opportunity for ion therapy. And this is why we have decided, back in 2018, to make an effort to work to reduce the size and cost of the accelerator for ion therapy, and also to promote the construction of new centres, not only for therapy with ions, but also for research. Because as you've seen, the four centres now operating in Europe are mostly worth, most of their time is used to treat patients. There is little time for research, where instead research is essential at this stage, if you really want to optimise the tools for ion therapy. So, we started to work on the accelerator, but not only to make it smaller, let's say, but also to exploit recent advances in radiation therapy itself. For example, there is a lot of excitement in the field of radiation therapy, about FLASH radiotherapy. FLASH is simply giving the dose in a very short time using ultra-high dose rates, and there is now quite a lot of evidence that such high-dose rates can spare the healthy tissue compared to conventional radiotherapy without reducing the damage to cancerous cells. So, basically, it's a similar effect of what you can do with protons and ions, thanks to the ultra-high dose rate. But you can couple proton and ion therapy with FLASH, and then, you have the best of both worlds, because really you would have a tool that has a minimum impact on the healthy organs around the tumour. But so far, particle accelerators can do only tests with FLASH because the technology does not allow to do FLASH on medical scale, on treatment scale for the volume usually taken by a tumour. So, you can do tests on small volumes, but you cannot, with the present technology, do a full treatment with FLASH. And so, this is something that also we are going to incorporate in our future designs for ion therapy machines. And then, there is also the option of using multiple ions at the same time for treatment, to do a better treatment, and also, possibly for imaging. And this is the origin of our initiative that is called the Next Ion Medical Machine Study, as you have seen in the title of this lecture. We are glad that we are working in a large international collaboration. We have a lot of partners and we have structured this collaboration a bit like our scientific collaborations. Very open, very collaborative, and for the moment, really very glad of how we are operating and of the initial results that we are getting. So, where are we working? Basically, in three directions. The first is the design of small synchrotrons. It's a challenge, because at CERN we know very well how to build something which is big and expensive, but to make it small and cheap, it's an art in itself. You need a lot of theory analysis, and now, we are really going in this direction to see how we can miniaturise this accelerator. The second technology that we are exploring is superconductivity. Superconductivity is already used in cyclotrons for therapy, for example, but now we want to use it in synchrotrons for ion therapy. And there again, we want to use not... A superconductor does not dissipate power. A superconductive magnet does not dissipate power, but when operating at temperatures close to the absolute zero, the advantage is not so much in the power dissipation, is that you can increase the magnetic field. So, you can accelerate higher energies in a small size. And then, the third point for our development is the gantry. You've seen the huge dimensions of the gantry in Heidelberg, and this is something that we really want to make that now to use superconductivity to reduce the size of the magnet. Here you see some examples of what you can do with magnets, going from the big 15-metre magnet of the Large Hadron Collider. We have about 1.200 of these installed in a tunnel here in the Geneva area, but they are more or less straight. A small synchrotron needs a heavily curved magnet with a very precise field because medicine requires a precision that is even higher of the precision that we need for particle physics. So, really, the control of the field here is actually very important, and then, operation of these magnets in fast mode, which is completely different from [Audio Not Clear]. So, it's also a big step, a big development and we have been fortunate because we have got the support from the European Commission for two projects, European-funded project, HITRI+ plus and I. FAST, and the goal of these projects is to have a first set of demonstrator magnets in three years from now. So, in three years from now, we will have ingredients that can be used to design, to assemble the first small superconducting synchrotrons. You see here some examples, and our goal is to come to a facility like this one where you can have a small superconducting synchrotron, and a superconducting gantry in about 1.000 square metre at a cost that is a fraction of the present cost for ion therapy. This is very similar to what our colleagues in Japan are doing, and here you see a similar concept that comes from HIMAC in Japan, where also they are working to the next-generation ion therapy, but even they have a concept for the next generation where they hope to come to something really small, but it's not really for now. This is really for the far future. Here, I have an example of how would it look like a gantry for delivery of the beam to the patients using superconducting magnets. You see here, and you see here the patient, and it's also an innovative design that we have just completed, and now, we are going to the production phase of the prototype magnets in the next year. It's also a large collaboration where CERN is one of the partners, but you see many other laboratories and universities involved. Here, I have another stop for questions. If there is nothing, Luca, I can go on.

Dr Bertolaccini: No, you can go.

Dr Vretenar: Okay, I go ahead to the last part of my presentation. We are coming to the end, where I would present a little bit the initiatives that are ongoing in Europe to promote and to propel ion therapy. First of all, one of the European projects I mentioned before, the HITRI+ is heavy ion therapy research integration, is really a project to support all aspects of heavy ion therapy. Clinical, access to research, but also networking, also clinical with, you see here, 18 partners all over Europe. But here, what I want to advertise is our transnational access. So, through the website of HITRI+, you can ask for access to the ion therapy facilities, the four ion therapy facilities in Europe, and to a laboratory for ion therapy in Darmstadt in Germany. For clinical access to refer patients to hadron therapy facilities and for research access to do research related to heavy ion therapy on one of the existing therapy centres. All this with some support from the European Commission. Then, I want to present another interesting initiative that has not only a medical aspect, but also a political dimension, the SEEIIST initiative. SEEIIST stands for Southeast Europe International Institute for Sustainable Technologies, and their goal is to build a large facility for cancer therapy and research with ions. So, 50% of the time operation for patient treatment and 50% for research in the Southeast of Europe. That means the Balkans, plus Greece and Bulgaria. So, this is a support from the European Commission and their goal is to build strategic operation, hopefully, in 10 years from now, less than 10 years from now, of a unique facility based on the synchrotron, still with the conventional warm magnets, not superconducting, but with many features that would allow really a step forward with respect to the present facilities for ion therapy. Here you see a bird's view of the centre with the roof removed to see the synchrotron, the gantry, and the treatment and experimental rooms. Then, I just want to mention very quickly that our British colleagues are very active in also developing modern advanced technologies for ion therapy. They have a concept which is called LhARA. At the moment, they are seeking funding through the UK Research Agency, and they are so advanced and so modern with the accelerator that in the first step, they don't even plan to treat patients. The stability, reliability and precision required for treating patients is so high that they prefer to start with the research, and then, after the first experience in exploiting this accelerator for research, they want to use it for patient treatment. And now, I come to my last technical slide to show another idea on which we are working, is that instead of using carbon that is very expensive to produce, as you've seen, there might be an intermediate way, opportunity between protons and carbon, that is helium. Helium is a nice ion with only two protons and two neutrons, so, is better than pros in terms of accuracy in depositing the dose. It's much more precise than protons and might be effective of some radioresistant tumours as carbon, but would allow, can be produced by a much smaller machine. You see a small synchrotron of about seven by nine metres, and that is a small facility for research and treatment. And there is already some interest from the Baltic scientific community for a new Advanced Particle Therapy Centre of the Baltic States, so Estonia, Latvia, and Lithuania. So, we are working on them on the different options for this helium synchrotron. And now, I come to my conclusions. So, my conclusion, the messages that I want to pass you in this lecture is that ion therapy is still in its infancy. So, there is still a lot of work to do to improve the treatment and to get more clinical experience with ion therapy. However, the goal of ion therapy is not to replace X-ray therapy or even proton therapy. The goal is to add to the arsenal of advanced instruments to treat cancer. So, simply, is make to the medical community a new tool available in the fight against cancer at a reasonable cost, at an affordable cost. The main directions for improvements to improve ion therapy are, of course, smaller, less expensive accelerators based on the most advanced technologies. Superconductivity, for example, but also precise online imaging and accurate beam positioning. With compensation for organs in motion, and integrating multiple ions, FLASH beams, and other different options for beam delivery that would really allow us to find some optimum performance. And finally, accelerators can provide, thanks to their capability to act on the atomic level, really breakthroughs in particle therapy. But again, in conjunction with a robust experimental programme. So, we need to know more, we need more experimental evidence on particle ion therapy, and we need facilities that can devote a large fraction of their time to research. Finally, physics laboratories like CERN can give their small, humble contribution, not only with some competencies in physics and technologies, but also acting as an aggregation point for wide international and multidisciplinary collaboration. This, I think, is something that is in our DNA of physicists, and this is something where we can really, we look forward to working with the biological, biophysics, and medical community. And on this, I thank of your attention and I'm here to answer your questions. Thank you.

Dr Bertolaccini: Thank you, Professor Vretenar. Thank you, Maurizio, for this presentation this afternoon during the European School of Oncology session. You have presented the future, or the next future. So, we collected some questions. Some points of discussion. The first is about the curiosity of CERN and medicine, and some attendees ask when started the interest of CERN for medicine? In the last year, in the past?

Dr Vretenar: Oh, let's say from, really, almost from the very beginning, from the '60s and '70s. At a personal level, many colleagues started already to work on problems related to medicine. Real engagement of the laboratory started only in the '80s and '90s. And in the '90s, actually, CERN was the origin of the developments that brought the construction of two of the four European ion therapy centres. So, this was a big effort between '95 and 2000. Then, there was much less, basically because everybody was busy building the LHC and looking for the Higgs Boson. And now, now that we have the Higgs Boson, we have time to think to the future and also, to other activities, and there has been a revamping of medical studies.

Dr Bertolaccini: Okay. Another question is, if you could describe another time the advantages of heavier ions in therapy.

Dr Vretenar: Yes, so first of all, as you see, so the peak, the Bragg Peak is sharper. The higher, the heavier the ion, the sharper the peak. So, you have more precision, let's say, in your instrument with respect to protons or other ions. Yes. Second is that the type of biological action on the cells is completely different with heavier ions with respect to lighter, like, protons, because really the heavy ions, they destroy the DNA of the cells. They destroy the DNA of the cells; they have a different action on the cell. While protons and X-rays act on the metabolism of oxygen, in this way, they kill the cell. With the ions, you kill directly the DNA, so, they are effective on radioresistant tumours. And on top of that, breaking the DNA, you create radicals. That seems to have an effect combined with immunotherapy in treating also, an effect on diffused cancer. So, it's a very promising direction for using these ions. And so, we now work with carbon, but already I have colleagues that ask for more, so, maybe the next-next-generation will be beyond carbon, even heavier ions.

Dr Bertolaccini: Okay. So, let's move to the next-generation with some questions about the cost estimation. Have you done a cost estimate of this machine? You say 200 million Euros for the past machine, but for the next?

Dr Vretenar: We have, let's say, half is the goal.

Dr Bertolaccini: Okay.

Dr Vretenar: Okay, of course, it depends also on how many treatment rooms you have, how many gantries you have. So, on the accelerator itself, you can gain maybe 20, 30% of the cost, yes. For example, with superconductivity, yes. Then, you have the saving on the building, on the shielding, so, altogether, and on the gantry. So, altogether, I think that the goal is a factor of two.

Dr Bertolaccini: Okay. The dimensions are really smaller between the past. So, the possibility to construct outside a big city. There is the possibility, you do not need another city to build.

Dr Vretenar: No, no, but for example, even the existing synchrotron for ion therapy in Heidelberg is built inside the hospital. So, it's on the premises of the hospital. And now, this will be more and more possible, I mean, if you make a smaller accelerator.

Dr Bertolaccini: And speaking about the energy need to this technology, how much is the energy needed to perform a treatment?

Dr Vretenar: Energy of the particles? Or power consumption?

Dr Bertolaccini: I think power consumption.

Dr Vretenar: Very good question, because we are also working on that. So, of course, I didn't have time to treat all the subjects we are covering with our study, but at the moment, the consumption of a synchrotron is of about 400 kilowatts. In operation.

Dr Bertolaccini: Okay.

Dr Vretenar: Yes, so these numbers are fresh in my mind, because I was looking at it yesterday. And we are actually also working there to reduce by factor of two, maybe something of that order, because we have identified some drivers for power consumption where we try to work. Unfortunately, we were hoping that superconductivity helped. In fact, it does not so much, so, we don't gain much going to superconductivity. You would gain other things.

Dr Bertolaccini: There are a lot of comments about the quality of life for patients, and a lot of comments are that the next- generation could be really quality of life, a treatment with a better quality of life. But there is the problem of the hub-and-spoke system because, yes, it could be only one centre between three or four nations, I think, so. Or one for nation. So, there is the mobility of the patient that was a problem during these pandemic years.

Dr Vretenar: Yes, yes, yes, yes, yes. So, okay, thank you for raising two very important points, yes. So, actually, the quality of life is our goal in this sense, because all these techniques that aim at sparing the healthy tissue, basically going in the direction of improving quality of life after the treatment. And they suggested that now people, they don't want only to survive, they also would like to live, to make as much as possible a normal life after treatment. And so, this goes in this direction. About the size of the population for a carbon ion machine. Now, if you consider only the radioresistant tumours, then, the conclusion is that one or two machines per country are sufficient. But if, as we hope, you can show that there are other advantages of using ion therapy, and if you can combine ion therapy with FLASH therapy, then, this would change the data and would change the numbers. So, at the moment, you don't need many of these facilities. On the other hand, making it smaller and cheaper would make also easier moving patients around. And by the way, this is also one of the reasons why we are working on the helium synchrotron machine. Now, on helium. Helium is now, in Heidelberg they just started patient treatment with helium. The first patient was treated in September last year, and it's a very good, let's say, direction to have more a network of machines that give you some of the advantages of ion therapy without the cost.

Dr Bertolaccini: Okay. You say the machine in Heidelberg, in Pavia and so on, but in the US?

Dr Vretenar: The US, you know that everything is dominated by the health insurance companies, and so far, they have refused to go to ion therapy. So, US patients go to Japan where they have really many facilities installed. Japan, China is also going in the direction of ion therapy, but really Japan is the pioneer in ion therapy, yes. Now, apparently it has changed because it's been announced that the US is going to build its first ion therapy centre.

Dr Bertolaccini: Okay. And in the last question, it's a little bit provocative and say, Professor, but the industry, when knocked to your door?

Dr Vretenar: Yes, it's also a good question. Already they knock at our door, or they say we bring them in for the development of the superconducting magnets. So, the demonstrators are going to build in-industry, by industry inside these European projects. Actually, we try to go as far as we can in collaboration with industry, co-innovation before giving them the access to the technology. So, this is the first step. Then, the next step will be when we really build the synchrotron, then we really need partnership with companies that have experience in medical products. Medical certification is one of the concerns, but we are still a few years away from that.

Dr Bertolaccini: Another question. Do you want to try this machine on what model? What animal model?

Dr Vretenar: I don't understand the question. You mean animal?

Dr Bertolaccini: In the experimental phase, the machine should be...

Dr Vretenar: Testing on animals.

Dr Bertolaccini: Tried on an animal model. Sheep. Or monkeys?

Dr Vretenar: Yes, yes, okay. So far, this has been used on pigs.

Dr Bertolaccini: Okay.

Dr Vretenar: Yes, so far pigs have been used for the accelerator that have been developed so far. I think that this is the best model for testing these machines.

Dr Bertolaccini: Okay. Thank you so much to Professor Vretenar from the CERN. And thank you for this presentation. It was really a great pleasure for me, and for the European School of Oncology to have you this afternoon. So, thank you to all the attendees. Maurizio, if you want to close?

Dr Vretenar: It was a great pleasure for me too. I really appreciated the very pertinent questions and the time that I spent with you, and I'm available if you have any additional question by email, I think that you'll be contacted. So, I will be pleased in the limit of my time availabilities to answer your question. I'm very happy to get in touch with your community, that is really fascinating. Okay, thank you very much again, for this invitation.