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Particle accelerators for cancer therapy: overview and recent trends

Dr Vretenar: Good afternoon or good morning or good evening, depending on the continent from where you are following this lecture. So, the subject today is "Particle accelerators for cancer therapy: overview and recent trends." And all what I show is somehow based on the work that we are doing at CERN, in collaboration with about 20 university research centres on applications of accelerators in medicine, and in particular, for the treatment of cancer. Particle accelerators, I think that you all know them as the most advanced scientific instruments ever built by humanity. Definitely, the largest, and here at CERN, we have the privilege of having the largest accelerator ever built, the Large Hadron Collider, 27-km. So, here you see a view of the tunnel of the HC, a number of elements, and it is at 100-m. underground. So, this is the largest accelerator for science, but we have to consider that only a minority of accelerators are used for science. Definitely, the largest ones, but there are thousands of small accelerators in many places helping with industry and with medicine. And in terms of number, medicine is the largest user of particle accelerators. And now, we'll go to see how and where these accelerators are used. But first of all, what is a particle accelerator? How do they work? What is their function? Actually, all the physics that you need to know to understand particle accelerators is here. You just have to remember that an atom is made of nucleus, that is made of protons and neutrons that are quite heavy. And only protons have an electric charge, and around this nucleus are the electrons that are in an orbit around the nucleus. Electrons are much lighter. It is relatively easy to extract the protons and electrons from an atom and a bit more difficult is to accelerate them. So, a particle accelerator is an instrument that gives energy, a lot of energy, to these particles. And then, you send these particles against another atom, against the atom. Basically, you are concentrating huge amounts of energy in very small volumes and when you send this, what we call a beam of particles, onto an atom, you can have many effects. You can kick out the electrons, so you can produce electrons. These electrons can produce X-rays or you can interact directly with the nucleus. You can activate the nucleus, the nucleus can become radioactive and then can decay, producing different types of radiation. And eventually with machines like the Large Hadron Collider, you can even create new particles, break particles, and create new particles. But it is not used in medicine, at least for this century, maybe the next one.

Now let's go to look a bit more in detail what you can do with a particle beam. A beam of particles is like a small knife that can penetrate into the matter. And here I say penetrate because you can go deep into the matter. A laser, for example, is also something that can concentrate a lot of energy, but lasers do not go in-depth. Sometimes, most of the energy is reflected by the surface, and instead, particle beams can go inside and not only but heavier particles, like protons or ions that are basically nuclei of atoms, can deposit most of their energy at a very defined position inside the body, or inside the tissue, inside an element. So, energy can be delivered. So, we concentrate a lot of energy and we can deliver it at a very defined area inside, for example, inside the body. So, this is why particle beams can be used in medical applications, in industry, to cure cancer, to kill bacteria, to treat materials, plastics for example, but also to dope semiconductors, a lot of applications. By the way, there is one remark to be made, if you think that you can use these beams of particles to make a weapon, they're not very effective because to propagate a beam of particles needs a very high vacuum. So, I need to accelerate, to send my beam in the vacuum and in the air, it is almost immediately lost. This is why for example, if you want to treat a patient with a beam of particles, the patient has to be very, very close to the accelerator, so to minimise to a few centimetres the distance that the beam has to follow... has to cover in air.

Okay, but where do we use in particular accelerators in medicine? This is a small cartoon that I have made that shows all the different applications of accelerators for medicine. Basically, they can be used for cancer treatment and for imaging. And these type of applications are divided into three main categories. First of all, you can send your particle beams directly on the patient and then, you have different effects, consider if you're using protons, ions, I mean nuclei, or electrons. Therapy with protons and ions is sometimes called hadron therapy. A hadron for a physicist is a heavy particle, proton or ion. Or you can send directly the electrons. And here you have different types of therapy. We will go into more details about that. Otherwise, what you can do, you can send your beam on a piece of metal, something we call a target, where the particles excite the electrons that create X-rays or even neutrons. And X-rays produced by a beam of electrons on a target are used in radiation therapy. This is the largest use of particle accelerators, it's in conventional radiation therapy. X-rays produced by a beam of electrons, about 14.000 machines installed worldwide. Then, there are some smaller applications with neutrons and then there is the big field of using radioisotopes. Radioisotopes are produced on the target, are activated nuclei that then decay producing radiation. So, you have the time to transport your radioisotopes from the place where they're produced to the hospital where they can be used for imaging. So, the different tomographies using radioisotopes are really also widely used, we use everywhere, practically in every hospital. And then, there are more modern ways of using these radioisotopes also for treatment and for combined treatment and imaging that is called theragnostics.

So, a large number of applications, many applications, what do they have in common? Let's say that in general every technology starts from a dream. So, you want to do something and you invent the technology to do it. And here the dream is always the same, is bloodless surgery and imaging. The old human dream of entering into the body to see inside and to treat, to cure without pouring blood. And this is something that is possible only thanks to the penetration of the particle beams inside the body. So, now that we have seen that, I come back to the most successful particle accelerator that is used in medicine, which is the conventional system, system that is used for radiation therapy. It is something that is around since, say, 30 years, 20-30 years that these types of machines are widely used. And you see that inside the radiation therapy Linac, which is called, there is a small accelerator, about 1-2 metres of accelerator, for electrons and then the beam of electrons is sent on a metallic target where the electrons produce X-rays. It is what we use for radiation therapy. From the point of view of accelerators, this is a wonderful device because this type of accelerator is conceptually very complicated. So, there are books of theory to explain how this kind of things work but mechanically it is very simple. So, it's ideal to be used in the medical system because it's very robust, reliable but conceptually it is really very sophisticated. Okay, having said that, now radiotherapy is progressing very quickly. You see the examples of therapy from different angles, collimators that are used to reproduce exactly the shape of a tumour to minimise the dose outside of the tumour, combination of imaging and treatment. So, there is a lot of progress but there is also a way to go beyond conventional radiation therapy with X-rays that is treating cancer directly with particle beams. So, the goal is here to treat the cancers that are considered, let's say not curable, so large, deep seated, and sometimes radioresistant. And for particle therapy, at the moment, the standard particles are protons or carbon ions, ions a bit heavier than protons, are the only two that are certified for treatment, the only two particles certified for treatment at the moment. The challenge is to use the Bragg peak, that I repeated here, to deposit the dose on the cancer, sparing the surrounding tissues. And this means that the power of particle beams is that they can be used... they are used for example for paediatric cancers because the risk of recurrences is much, much lower using particles than using X-rays, for typically brain and head-and-neck tumours that are very close to critical organs, and in particular ions are used for radioresistant tumours that are resistant to X-rays. So, nowadays, so I'm not a clinician, so here simply I show a slide I've got from our medical physicist. And those are indications from the ASTRO, Association of Radiation Oncologists of US, that have divided... that identified cancers in two groups. The first group are those where treatment with protons, this is all for protons, this treatment is recommended based on established clinical data, and you see here a long list of tumours. And then, there is a second group where clinical data and effectiveness, comparisons are ongoing, are based on ongoing clinical trials. But as time goes by, more and more cancers go from group two to group one and more and more cancers appear in group two. Here you see an example for a spine treatment, the comparison between X-rays and protons. So, it's going very rapidly in numbers. In terms of facilities in operation, you see that starting from the year 2000, the last 20 years, we went from 15 to 150 particle therapy systems, most of them are with protons, only 14 nowadays operate with heavier ions. From the first, you see, the first experimental treatments were started only in the 90s in the US, then, Japan somehow took the lead. And in Europe, we followed with first treatments at scientific centres during the 90s and only from the early 2000s we start to have more and more facilities in hospitals often dedicated specifically to treatment with particles.

So, protons, as I said, at the moment more than 90% of the particle therapy centres are working with protons. Why? Because proton accelerators are very simple. So, the workhorse of proton therapy is a type of accelerator that we call the cyclotron. You see this is an example of a cyclotron-based system. The cyclotron itself is very small, these are the beam lines. And what is big here is the gantry, a rotating gantry that is used to move the beam around the patient and target a specific angle on the patient for the treatment. So, on the market now you find a number of companies selling proton therapy systems that can be single room, this is an example of a single room centre or multiple-room. So, very successful but nevertheless there are some limitations, limits to the treatment with protons and to the type of machines that we are using. From the point of view of the accelerator, one of the issues is that a cyclotron is a machine that is naturally at fixed energy. And if you want to scan longitudinally a tumour, you need to change the energy of the beam to move the Bragg peak inside the tumour. And this is done in cyclotrons with simply, mechanically, blocks of metal that enter in and out to intercept the particle beam. This is slow and has many issues of radiation. So, this place becomes quickly radioactive, which is something that is not the best for the operation of the machine. And then, if the cyclotron is very effective for protons, the more you go to heavier ions, you need higher energies. And for higher energies, cyclotrons become less effective. At the other end, so I said that protons are certified for treatment and also heavier ions like carbon ions, carbon is much heavier than the proton. And here, you see an example of two centres that have been built for therapy with carbon ions, one in Heidelberg and the other in Pavia, in Italy. And to give an idea of the dimensions, this is the patient lying on his couch, and this is the huge gantry that sends the carbon beam onto the patient. So, this is a big system with the cost of one or two hundred millions in the construction but at the moment is the only way to reliably deliver treatment with heavy particles. But why do we need heavy particles? We need them because, you see, so the comparison between X-ray, a proton, and a carbon ion, that has a mass that is 12 times the mass of the proton, simply because you have a higher energy deposition from heavier particles. So, you create many non-reparable, double-strand DNA breakings. So, you act at the level of the DNA, while the protons act at the level of the oxygen metabolism of the cells, the action of the heavy ions is different and this is why they are active, effective also with radioresistant tumours. So, the mechanism is the same between X-rays and protons, let's say, only the dose distribution is different, but for ions the mechanism is different. And then, there are also indications that in combination with immunotherapy, ion treatment can be also useful to treat diffused cancer and metastasis. So, there are a lot of expectations from heavy ions, but heavy ions are heavy, by definition, and what is heavy is expensive to get. And here, you see, let's say, a comparison of size and cost between accelerator designs for X-rays, a conventional Linac, a few million euros, a cyclotron for protons, a few tens of million euros, and something to the order of a couple of hundred million euros for heavy ions. Clearly, not all healthcare systems can afford going in this way and for the moment heavy ions remain a niche, let's say, in the particle treatment. But the situation is evolving very rapidly and the next step, the next chapter of my lecture will deal with the new trends in the particle therapy of cancer. So, we are conscious that there are limitations in the present system, that particle therapy systems are expensive. And so, there is a lot of work to see how this can be simplified and how particle therapy can be made more accessible.

One very popular let's say subject in this moment is FLASH. FLASH irradiation is due to the recent re-discovery of an effect that was already observed in the 70s and was re-discovered in 2014 at the Institut Curie in France. Simply, the observation is that if the radiation dose is applied very rapidly, then there is no effect on the healthy tissues while the effect on the cancerous cells is the same as when the dose is applied slowly. So, to give you an idea, usually in conventional treatments, the radiation dose is applied in several minutes. FLASH treatment instead goes to fractions of a second, hundreds of milliseconds. So, it's a factor 10, to the power of 3, to the power of 4, faster in the application of the dose. And here you have a famous photograph from the Vozenin first papers where you see the skin of a pig, that is, where the same dose is sent conventionally, slowly, and you see the damage to the skin, and instead FLASH so rapidly that you don't see any visible effect on the skin. It's an interesting effect. Interesting also because it's a threshold effect. It's not that the faster you go with delivering your dose, the less is the effect on the healthy cells. There is a threshold, up to a certain moment you don't see difference, and when you are faster than a certain value, it depends on the type of particle, it depends on the type of tissue, it depends on the energy, then you observe the FLASH effect. So, there is a lot of work now going on worldwide and the first patient with a skin cancer was treated only in 2020, so it's a really very fast.

Now, there is a lot of work going on in using what is available in terms of electron and X-ray beams and proton beams for FLASH. The point is that you need a high-intensity that present machines cannot deliver. Of course, if you want to give a dose very rapidly, you need a huge, let's say, the flow must be very high. So, it's you need a more powerful machine to deliver it. There are many issues of dosimetry because, for example, if it is so fast, how can you measure the dose? And there, of course, the point is how to deliver this very powerful dose on a large tumour. So, there are many issues to be solved so that at the moment the experiments are only limited to small tumours and on the skin. But now, there is work going on designing and building a FLASH therapy electron machine that can go to deep, can treat deep cancers. Electrons, they use electrons because they are more effective than X-rays for FLASH. And the machine is considered to be simpler than a proton machine for FLASH. To be demonstrated, actually, but what is interesting is that now there are in Europe three teams that are really working hard to build the first electron FLASH accelerator that is going to be used first of all for experiments, clinical trials, and one day maybe for treatment. One team, CERN, with the University Hospital of Lausanne and the company, another at Institut Curie in France with another French company, and then there is a team led by the Rome University that is also designing now a FLASH therapy accelerator and is now contacting a number of companies to find an industrial partner. And here you see a scheme of the CERN system that is now in the advanced phase of design, you see here. At the FLASH conference, a few months ago, there was a debate where they asked all the radiation oncologists present "what do you think is the future for FLASH?" Of course, everybody was seeing a bright future for FLASH and they voted what is the most promising particle for FLASH? You see that there is no agreement. There were almost one third, one third, one third between X-rays, sorry, protons, electrons, and X-rays or photons, only in the second vote there was a slim majority for electrons. So, it'll be interesting to see what will happen in the next years, but there is not only FLASH, we are also working at another idea for delivering a very precise particle treatment to cancer that is using helium beams. Helium, it's, you see here, a nucleus of helium is two protons and two neutrons. So, it's not as heavy as carbon but it is still four times heavier than protons and the cost of the accelerator is less than one half of a carbon machine. So, it's something really in between. And helium is the most precise machine, in terms of conformality is the best particle, in terms of conformality, and is much less expensive, it is only slightly more expensive to produce than protons and is much less expensive than carbon. And you see here example of a Bragg peak, as it is called, spread out. So already after this longitudinal treatment, treatment of a longitudinal slice of a cancer, and you see in the curves that helium is much better than protons at the entrance and is also much better than carbon after the tumour. So, no comparison with these photons and X-rays, and this is a typical curve of a standard conventional radiotherapy Linac. So, there are a lot of expectations about helium.

Recently our colleagues from Heidelberg, from the Heidelberg Hospital and Medical Centre and the Heidelberg Ion Therapy Centre have published a roadmap for helium therapy that is a kind of vision on how one is to go from the present experimentation with helium to widely using helium for cancer treatment. So, lot of expectations and this pushed us to design an accelerator for helium, which is based on the small synchrotron. You see a triangle, it's not even a circle, 10 metres only of synchrotron with two lines, one for static treatment at another equipped with a gantry. And here you see an image, so you see this is the person, and these are the magnets of the small accelerator and the synchrotron is fed by a linear injector that can also produce radioisotopes. And by the way, this machine is from the beginning capable of FLASH operation. So, we want to combine the benefits of helium with the benefits of FLASH to make helium FLASH. There is interest for... so here you see how a facility based on this machine would look like, so, about 2000 square metres and there is interest from the Baltic states, Estonia, Latvia, Lithuania, to build a combined particle therapy centre in the region that would use this machine. Start with a standard treatment programme with protons, if you can do helium, you can also do protons, all what is lighter you can do, so you can do protons and then, go to experimentation with helium and possibly, treatment, one day, with helium. Here you see the gantry, how it looks like, this one here for distribution of the beam to the patient.

Okay, I said that this linear injector could also produce radioisotopes because I want to open a small parenthesis on the use of radioisotopes in particular for treatment. So, nowadays, we have many accelerators producing radioisotopes for imaging but few that produce experimental radioisotopes for treatment of cancer. In particular, for this helium machine you produce radioisotopes using helium beams and in particular you can use alpha emitters. Okay, sorry, here I have to change a bit my vocabulary because so far I was speaking of helium ions, and a helium nucleus is an alpha particle. There's always two ways to call the same object. An alpha particle is what in the past was called a nucleus of helium, so two protons and two neutrons. And alpha particles are the most dangerous radiation because they have high toxicity to the body, they kill the cells immediately but they have a very short range, they penetrate in the tissues only for microns. So, if you can introduce an isotope that emits alpha particles on the tumour itself, then it would immediately kill the tumour. And this is why there is a lot of work going on what is called targeted alpha therapy that can use alpha emitters, like, for example, a wonderful atomic element that is astatine. Astatine is the most unstable element on the periodic table. You can produce it only in an accelerator and basically you give your alpha particle to the astatine, and then gives it back. For example, inside the patient, if you can attach your alpha emitter to a targeting vector, an antibody, a peptide that sticks on the tumour. So, here you understand that the challenge is not so much for the nuclear medicine, the challenge is for the radio chemistry, to find the right targeting vector to carry this alpha emitter to the patient. But there is one more interesting, even more interesting, way to do this that I want to mention, is the Boron Neutron Capture Therapy, which is really a wonderful application of modern nuclear medicine because you can, instead of using astatine, with your accelerator you can produce boron, you can produce neutrons and you can inject into your patient an isotope of boron that is not radioactive, so very stable but becomes reactive only when it is bombarded by a beam of neutrons. And this is a technique that starts to be used, for example, for treating brain tumours, glioblastomas and others like malignant melanomas. Again, the Japanese are the most advanced in this type of technique. They have 7 centres in Japan and two are just completing clinical trials, and you see how the system would look like, an accelerator, the proton beam generates a neutron beam, and the neutron beam hits, for example, the patient in this region. And even if the boron is a bit everywhere in the body but only in the region it is activated by the neutron beam, the boron becomes radioactive and produces the dangerous alpha particles. Nowadays, so Japan has the lead but in Europe we have one centre for this therapy, there is a construction in Finland and two more are in design/construction in Italy. So, one at Pavia, at CNAO, and I learned last week that there is another one which is going to be built at the Caserta Hospital, by the way, with the money of the recovery fund, of recovery Europe, so it's a very recent venture. Okay, and now it's time to come to my last slide.

So, we are talking about radiation therapy, proton therapy, FLASH, ion therapy, targeted alpha therapy, immunotherapy. What is going to be the future? The answer is, of course, I don't know. But there are a few concepts that I would like to pass you. First of all that medicine is really becoming the technology driver of the 21st century. So, it's something we see clearly in our laboratories, that there are many demands from medicine and also the most sophisticated and interesting sometimes problems come from medicine. So, it's really, the main... the challenges for technology nowadays, most of the challenges are coming from medicine. Let's hope that we stay like that after this war but this is the case nowadays. Second is that all the techniques that we are studying are in a sense complementary. So, I don't believe that one day we'll have one that will kill all the others but we'll go more and more towards a personalised medicine where we have really a full arsenal of instruments that are going to be available for the cancer expert. And then, the trend is, of course, technology will go more and more towards compact systems that are controlled by artificial intelligence. So, I could make another lecture talking about what we can do, what marvellous things we can do with artificial intelligence for these sophisticated instruments and then that we'll act at the atomic and molecular level. So the point is that so far medicine was based on chemistry. Chemistry is what led to our modern medicine, but now is the time to go beyond, and nuclear medicine, that acts at the level of atoms and molecules, I believe, has a bright future. So, clearly nowadays, what we see are big systems that are very expensive, very experimental, but we have to understand that what is advanced medicine today will be standard clinical practise tomorrow. And on this, I thank you for your attention.

Dr Bertolaccini: Thank you so much, Maurizio. We are really happy to have you after one year from your last presentation to show us the results and the change between one year. So, I have some questions, comments and so on about your presentation. The first it's a curiosity about CERN. So, CERN is not so only a theoretical research organisation, but also a medical research organisation. I know that the idea of the positron emission tomography was developed in CERN a lot of years ago, but we want to know, your group, how people really live and work inside CERN and try to research in the medical field?

Dr Vretenar: Okay, thank you for this question. So, I can say a few words on our problems and opportunities. So, as you say, I mean, the goal of CERN is to do particle physics and to build and maintain the big instruments for particle physics. But more and more, on the one hand, more and more we want to highlight what is the impact of our science on society. So, it is in the interest of CERN, let's say, really to show that what we do is not only for a few scientists but real applications of our technologies on society. And on the other hand, you have to think that only 3% of the CERN personnel are research physicists. All the others are technologists, engineers, people really working on technology and they have plenty of ideas, of course, on how they can really use their technologies. So, there is the opportunity of doing something. But of course, we are struggling with the fact that we are not a priority line for CERN. So, at the moment I have the privilege of coordinating or leading, let's say, a team of about 12 people that have all different origins. I'm the only one who is a staff member of CERN in the team. All the others are doctoral students, contributors from other universities. So, we have all different type of... it's a very disparate team, let's say, very international and working very well together. And we try really to get as much as we can. So, so far, I was very happy because at least we had one medical physicist in all CERN, can you imagine, a PhD student in my team. And today, I learned that we have a second one, today at lunchtime. So, you see, we take time really to grow this team because it's not in the priorities of CERN but it's something that is nevertheless very important for CERN where I think that we can have an impact but not alone, but in collaboration with others. So, we are looking for collaborations. We are too weak in a sense and it's not our main competence, medicine, this is why we need to work with others on that.

Dr Bertolaccini: Thank you, Maurizio. So, let's move to the medicine and for instance to the lung cancer treatment. In these recent years, the lung cancer treatment is moving versus immuno-target therapy. So, the role of the radiotherapy merged with the immunotherapy is really, really interesting because you said that we could share radiotherapy not also to early-stage or locally advanced stage, but also, to metastatic patients. Could you comment about this?

Dr Vretenar: Well, the experiments that are going-on on mice at the moment are based on the fact that with a beam of ions, you hit the tumour and you create bits of DNA that is then distributed inside the body. And with immuno, coupled with an immunotherapy drug, you can enhance the response of the organism to the radicals that are distributed inside the body. This is my... okay, I'm not an expert, so this is the kind of idea that I've got of this type of experiments, but at least on mice, they are very promising. Again, mainly they are done in Japan and by our colleagues at Albstadt that are very much advanced in this kind of experimentation. So, of course, there will be long time until this can be used on humans, but I think it's an interesting way of really using immunotherapy, coupling immunotherapy with particle therapy.

Dr Bertolaccini: So, let's move to the helium and talk about the roadmap. In your opinion, when the helium treatment could be used in clinical practise?

Dr Vretenar: Oh, then again, it's an exercise of the crystal ball, but let's say that already now the first patient has been treated at Heidelberg with helium, and licencing of helium, the work for licencing of helium is progressing at Heidelberg and Wiener Neustadt, in another carbon ion centre. So, I think a couple, one or two years, until we can have the first, the licencing and really the first clinical trials at Heidelberg and Vienna. Okay, then, until this type of machine will need probably 10 years from now to be ready, but it's made, is intended to exploit data, so let's say a couple of years for the licencing then, clinical trials and when finally, it goes into medical practice, then we have we want to be ready with this machine.

Dr Bertolaccini: Thank you, so, you say that helium machine needs not a large space, correct?

Dr Vretenar: Okay, all is relative. 2.200 square metres in this design.

Dr Bertolaccini: Okay, it's large.

Dr Vretenar: It's still large, yes. But I mean it can fit in the campus of the hospital, it's the main part.

Dr Bertolaccini: Okay.

Dr Vretenar: Because it has to be very close to the hospital.

Dr Bertolaccini: Yeah. And the cost of building like this one in the picture, more or less?

Dr Vretenar: The cost of the building itself you mean? Yes, oh, if I scale from what I have built here at CERN for particle physics could be maybe 10, 20 million.

Dr Bertolaccini: Okay.

Dr Vretenar: Then of course it depends if you consider also all the hospital type area that is going to be there. And also, the cost of the machine depends on how many lines you have, so if you want only one line, two lines, you can have or you can have three lines, you want the isotopes or not, so these things would change a lot the cost of the machine, so it's...

Dr Bertolaccini: Okay, and about the indication of alpha treatment, of alpha particles, you say solid cancer or a blood cancer. Do you know which solid cancer if...

Dr Vretenar: Sorry, you're speaking of alpha therapy or of helium therapy?

Dr Bertolaccini: Alpha therapy.

Dr Vretenar: Alpha therapy, yes. No, here I don't have really, I cannot give you more details unfortunately. I know that the clinical trials are ongoing and actually one has to look at the work of our Japanese colleagues in this direction, yes. And what I know is that for Boron Neutron Capture Therapy, they found, references in particular to glioblastomas and then melanomas.

Dr Bertolaccini: Okay, so, sometimes, colleagues ask to the surgeon or to the oncologist, what will be the future? And you stated what will be the future in your opinion. In my opinion, the future will be a really multidisciplinary approach. So, not also the physician, the MD, but also the biologist. And it's really important up to now with the immunotherapy, target therapy and so on the genetic system. And so, in the future the chemistry, and the physicist. So, the future will be really a multidisciplinary approach to cancer.

Dr Vretenar: Yes, I fully agree. It is also something that we see in science, that the progress is at the interface between disciplines. Now we went... we know a lot about medical physics, we know a lot about medicine, but in between there is still a lot to explore and a lot of work to do, and there are many, many things that we can do working together, on this I am also convinced.

Dr Bertolaccini: Thank you. Thank you all for the participation. We are really proud to have this afternoon Maurizio Vretenar from CERN, it was an honour for me to be your discussant, thank you for your friendly application to the e-ESO project. Thank you so much.

Dr Vretenar: It was my pleasure to participate and thank you so much for the invitation. Thank you very much.