LALITH K. KUMARASWARMY: Today, I'm going to talk about emerging technologies-- not only in radiation therapy, but cancer itself, OK? So the first couple of topics I'll be talking about is FLASH radiation therapy and minibeam radiation therapy. Then later on, I'll be talking-- I'll be veering off of radiation therapy and talking specifically about some of the technologies that are up and coming in cancer itself, such as nanoparticles and immunotherapy.

So what does-- one of the fundamental questions to ask? How can we improve radiation therapy. Well, you need to do two things. First thing is reducing side effects, and the second one is you need to make sure that you're delivering the radiation therapy more efficiently. If you focus on the first one, to reduce the side effects one of the things that we've been doing so far is that are reducing the margins. With an invention of IGRT and IMRT [INAUDIBLE] we're able to reduce the margins and treat less of normal tissue.

Another thing that we could focus on-- that is what I'm going to talk about in this talk today, or at least the first half of my talk-- is biologically, how can we reduce toxicity? Not only by reducing the margins, but in biological sense, how can we do this? So these up and coming techniques such as FLASH and minibeams will enable us to do that. And I'll be also explaining to you how in a biological chemistry-wise, how this is possible using these technologies.

So those are the two things that I'll be focusing on in the first half of my talk. Secondly, in terms of delivering radiation more efficiently, we could do adaptive radiotherapy, motion management, and also a new beam such as the carbon ion or even proton ions that Dr. [INAUDIBLE] talked about. But we could also focus on combining therapies, such as immunotherapy and radiation therapy, and also talk about nanoparticles, also. So in the second part I'll be more focusing on the immunotherapy part, and also some nanoparticles and nanobots.

So before I start talking about these technologies we need to understand one fundamental criteria in radiation therapy. So this criteria will help me explain it to you what I'm talking about, in terms of sparing normal tissue. So if you look at these two classical curves, these TCP-- Tumor Control Probability-- and normal tissue complication probability, with increasing dose, obviously they increase. So for example, if you deliver-- as the dose increases, the probability of tumor control also increases.

Likewise, if you increase the dose, the normal tissue complication also increases. So we need to figure out an optimal dose that will maximize tumor control, but at the same time reduce normal tissue complication. So for example, let's say if you choose a dose A, which is a very low dose, in that sense, we are eliminating normal tissue complication. But we're only about to control the tumor only about 10%.

What about if we say, you know what? I'm going to deliver such a large dose, such as dose C over here. In that case, we are controlling the tumor very well-- 100%. But at the same time, our normal tissue complication increases, right? It's about 80%. So that won't be good either, because now it's very toxic to the patient. So we need to find that balance.

So for example, here we chose this dose B, where you're only getting 10% of normal tissue complication while your tumor control is about 80%. So for in this instance, for conventional radiation therapy, dose B be the ideal choice. So the next two techniques-- other technologies I'd be talking about-- is primarily depending on these two-- this fundamental parameter.

So what is FLASH radiation therapy? So how many of you guys here heard about FLASH radiation therapy? Very good. Very good. Very good. OK. OK. So FLASH is mean this-- it's very ultra high dose radiation therapy. It's invented in France about two decades ago. So for example, if you look at a conventional radiation therapy, it delivers about 4 to 7 centigray per second. But in FLASH radiation therapy, you could deliver 5,000 centigray in one second.

So you could deliver about-- right now, they have technologies that could deliver even 100 to 200 gray per second. So for example, let's say a typical SPRT dose of 20 gray per second-- sorry, 20 gray per fraction-- in a conventional-- even with your flattening filter-free mod, it takes about eight minutes to deliver that treatment, beam on time. But with FLASH, you could deliver that in fraction of a second, OK?

So let's go back to this classical curve again. So remember we chose-- that for a conventional radiation therapy, we chose dose B. That gives you the optimal dose-- good tumor coverage and minimal normal tissue complication probability. But what FLASH radiotherapy does is that it moves your normal tissue complication curve more towards the right. So what it's essentially doing is that it's essentially-- your toxicity towards your normal tissue, it's reduced with FLASH radiation therapy.

So in that case, we could go back and deliver this high dose to our patient. So here, you're delivering a dose C, where you could have 100% tumor control while only having about 10% of your normal tissue complication probability. Now later on, I'll be explaining to you why-- in terms of biology and in terms of chemistry, why this is possible with FLASH.

So these inventors in France, they did a study. They want to see whether-- if this FLASH radiation therapy, how does it compare with conventional radiation therapy. So they did an animal study with mice. And they implanted these mice with these lung tumors on their back. And they had four groups.

First group did not have any implanted tumors, so they were normal mice. Second group had implanted tumors, but they did not receive any therapy. Third group, which had implanted tumors, but they delivered conventional radiation therapy. But the last group, they had tumors, but they were delivered with FLASH radiation therapy.

Now if you look at this diagram here, this goes down in timeline, OK? So day plus 8 means implantation radiation time plus 8 days. You could see the sham, which are the animals-- which are the mice who had implantation but didn't receive any radiation or any therapy, they died down after 14 days. With the conventional therapy, only two survived after about 35 days. But with the FLASH radiation therapy, almost all the mice survived, even after 62 days. About 70% of them survived.

So this shows that-- they were able to show with this experiment that FLASH radiation therapy not only controls tumor, but were able to control the normal tissue complication, as well. So if you look at the survival curve for these mice, you could see this is a control, which had no therapy. They died down pretty fast. But if we look at the FLASH radiation therapy, they survived for a much longer time as compared to conventional treatment.

So here's another study that was done recently. They weren't implanting any tumors in their mice. They just wanted to see whether if you take normal mice and if you radiate them with conventional RT and FLASH RT, how much would normal tissue will tolerate? So they were radiating their brain, and they were able to show that-- they were assessing whether FLASH RT altered their neurocognitive function as compared to conventional RT.

And they were found that FLASH RT with a dose of 10 gray delivered at 10 gray per second did not alter any neurocognitive function as compared to conventional RT. So this is another study that proves that FLASH radiation therapy able to protect normal tissue. And there's whole slew of study that was done on mice especially, and even in pigs, that they found that it was able to protect normal tissue.

Now comes the big question. Why is that? What is the mechanism behind it? Again, to understand that, we need to go back to a fundamental. So let's look back at one of the things that we all learned in school. It's called an oxygen effect OK? So as everybody know-- most people know that in the presence of oxygen, cells become radio sensitive, right? This is a classical curve that you've been seeing in the textbook. You have the survival curve versus the dose.

You could see the hypoxic cells, they don't die off as compared to well-aerated oxygenated cells, OK? So the bottom line is that hypoxic cells are radio resistant compared to normal aerated cells. So you could also talk about oxygen enhancement ratio, which says that ratio of dose administered under the hypoxia to aerated conditions needed to achieve the same biological effect.

So for-- OER for an X-ray, typical X-rays, is about 2.5 to 3.5. That means that for an hypoxic cell, you need two to three times more dose to kill that cell than a normal aerated cell. So that's what it means. So now, let's look at even more deeper. What does the mechanism of oxygen affect, right?

So you have a photon coming in into the cell and interacts with the water molecule, and it ionizes the water molecule. This ionization produces ion pairs. These ion pairs will go ahead and react and will produce free radicals. As you know, free radicals are very highly reactive. So these free radicals go, in turn, and damage your DNA. That's the fundamental process of DNA damage through radiation.

So now, in a normal cell, what happens is that they are able to repair this damage by this SH group. So they have other groups that they could come and repair this damage. So then they repair their damage and they could go on. But in the presence of oxygen, what happens is that oxygen comes and reacts with this damage site and makes that site permanent.

So none of these SH group cannot come and repair that site. So more oxygen you have, more it fixes that damage. So then, it becomes unrepairable. OK, so that's basically the oxygen effect. So what does that got to do with FLASH?

So when you are delivering such a high dose-- any radiation-- when you're delivering any type of radiation, it's going to consume oxygen. But in a conventional RT, when you're delivering dose with low dose rate, your blood could replenish the amount of oxygen that you have in your cells. So even though the radiation will gobble up all the oxygen, but the blood will replenish the oxygen.

But in a FLASH radiation therapy, since you're delivering such a high dose in such a short time, it takes all the oxygen away. So even your normal aerated cell becomes very hypoxic. This is one of the hypothesis that a lot of researchers are saying that this is why FLASH RT works. So now, if you have a hypoxic-- if you have a normal aerated cell surrounded by hypoxic tumor, with the FLASH radiation therapy, you're also making the normal cell hypoxic. So they also become very radio resistant. So that's why you are able to escalate the dose to such a high level to treat your tumor.

So FLASH RT in a summary, it reduces normal tissue toxicity by making your normal cells also hypoxic. So in that case, you could also deliver-- you could perform dose escalation. So for example, instead of delivering 70 gray for your tumor, because your dose is limited by your toxicity that you're delivering to your patient, so now even your normal tissue are becoming radio resistant. You could actually deliver even 100 gray-- even more to your patient with FLASH RT, OK?

So again-- so now another advantage is that since you're delivering such a high dose in just such a short amount of time, you don't have to really worry about motion management. You have to, but you just have to make sure that the tumor is localized properly before giving that zapping dose, OK?

So there are a lot of institutions working on a prototype LINACs that could deliver very fast radiation-- FLASH radiation. This Institute in Switzerland, they are developing this 6 to 5 MeV electron FLASH radiation therapy. So it's designed to produce a maximum peak current of 300 mA. If you compare that to a normal standard LINAC, only produces about one mA of current, whereas you need about 300 mA of current to produce for this FLASH radiation.

And this machine could deliver a dose of 200 gray per second, which is very high dose rate. Again, one of the drawback which a lot of them are working on is that you cannot put a standard ion chamber on the head of the machine to monitor the beam, because it's going to saturate your MRI chamber with such a high dose rate. So now they're working on some special probes that could actually monitor the beam that is coming out from the LINAC.

So the bottom line is that we are a long way away to producing a machine that could actually deliver safely to humans-- to our patients. To make that point clear, if you look at-- they were looking at the output of these machines over a period of 20 months. And you can see, the output varied drastically-- about plus or minus 10%. So there's a lot of work to be done to make these LINACs much more suitable and much more safer for patients.

Now what about protons? Well, protons have an advantage. I know Dr. [INAUDIBLE] talked about proton service you guys for a long time, but just as a summary slide, protons is very attractive for FLASH, because they are mostly forward peaked. So you don't have the lateral spread like you have for electrons. And you have the [INAUDIBLE] peak for photons. So that makes it much more attractive for photons rather than for electrons.

So UPENN is working on this proton machine which is FLASH capable. Right now, they are testing it. They are designing it specifically for animals. Here you see there's about 23 people working on this investigation. Here you have the beam line-- proton beam line. I know, it's very hard to see here. It's a very small image. But here, they place the animal in this cage. They sedate the animal, and they come up with this beam line just to treat the patient-- treat the animal. So this technology is still in very infancy stage.

So again, this is UPENN. What they want to do is that they wanted to see what the results would be if they could just take standard mice and irradiate the whole body of the mice with the FLASH as compared to conventional radiation. And they found was that with FLASH radiation, the mouse survived for a longer time as compared to conventional radiation.

So this is my first question. So FLASH RT, it can deliver dose rate up to 100 gray per second or even more. Number two, hypoxic cells are more radio sensitive than aerated cells. Number three, electrons are more suitable for FLASH, since they are more forward peaked than protons. Animal studies show that survival rate for FLASH is lower compared to with convention RT. Should be pretty simple.

Ah, very good. Very good. Everybody is listening. Good. I'm not putting too many people to sleep. OK. Good.

OK. As a summary of FLASH RT, FLASH RT demonstrates significant normal tissue sparing in animal studies. Biological effects and rationale for FLASH RT are still unclear, even though I gave you an explanation of why FLASH RT works in terms of oxygen effect. But there's still a lot of investigation going on in terms of really understanding what the biological effects are. And more research needs to be performed to improve deliverability and safety before starting human trials.

So next, I want to talk about microbeam radiation therapy. It is in the same line as FLASH RT, where you're delivering very high dose in a very short amount of time. But the difference is that instead of delivering uniform dose to your target, you're actually splitting it with a grid. So you have a very high peak and you have a very low peak. So it's not a uniform dose. So target will not deliver-- will receive a uniform dose.

This is, again, to reduce the toxicity of the normal tissue. So more research has been going on with brain lesions especially, because brain lesions are very hard to control, such as gliosarcoma and glioblastoma. So there's a lot of research going on, because it could reduce the normal tissue toxicity for these type of cases. So you could see a typical delivery here.

You have a high beam followed by a low peak, and high beam, and so on. So if you look at a typical conventional RT profile of an output, it's fairly flat-- symmetric. With the FLASH RT-- I mean, sorry-- for a microbeam RT, you have a very high peak followed by a very low peak. So the tumor will not be-- again, tumor will not be getting a uniform dose. OK.

So at this peak dose, ratio of this peak dose to this valley dose is called a peak to valley dose ratio, OK? The higher the peak to valley dose rate, the better the biological response. So for example, this graph here shows you a less effective microbeam radiation therapy, because it has a very high valley dose and adequate amount of peak dose. Whereas here, you have a very low valley dose and a very high peak dose. So the PVDR for this one is 10, and PVDR is 2.5. So this one is very effective compared to this one.

So microbeam radiation therapy spares normal tissue when the beam spacing is less than twice that of the beam width. And the sparing effect depends mostly on the valley dose and little on the peak dose. So what that means is that the normal tissue tolerance depends on this valley dose. So as long as your tolerance does not get exceeded by this valley dose, then you'll be the same as the conventional radiation therapy.

So your peak dose could be very high-- high as you want. But as long as the valley dose doesn't exceed your normal tissue tolerance, then you're OK. But this technology has been developed a long time ago, even in 1961. But unfortunately, they didn't have the technology to improve it or to make it available until now. So in thins-- in 1961, what they did was that they did a study. They delivered-- 140 gray was delivered with a wide beam and a middle microbeam and a very small microbeam. OK.

And what they were able to find was that with a wide beam, result in complete tissue destruction and cavity formation. Whereas the micro beam with a very small slit caused no damage with the 240 days observation period. Only after delivering 4,000 gray that there was-- they saw some toxicity in those animals. OK. That's at the high dose.

Here's another study that was done recently. They were looking at mice implanted with a very high grade carcinoma-- squamous cell carcinoma. It is very progressive disease. So they were able to show that with the control with no radiation, the survival dropped significantly. But with microbeam, the survival is much higher compared to a broad beam, like a conventional broad beam radiation therapy.

So the mean survival time with a broad beam is about 20 days for these animals. For the microbeam, it's about 41 days. So again, I'm trying-- this is one of the hypothesis of why microbeam works. There are a lot of other hypotheses, but I'm just going to explain one of them. So if you look at this picture here, this represent a vasculature for a typical tumor. It's fairly underdeveloped here-- very-- the capillaries for a tumor, it's not as developed as a normal tissue. So here, you see a capillaries for the normal tissue. There's well-- very developed. The blood supply is very good in this normal tissue, whereas in tumor tissue, it's very undeveloped, OK?

So now imagine when you're delivering microbeam for these two-- the tumor tissue here and all for the normal tissue here. So when you doing microbeam, it's like you're going in with a surgeon's scalpel. So you're just cutting off little portions of the cells, OK? So when you have an undeveloped cell, when you're going in and cutting off at certain areas, you're going to cut off the blood supply, and the nutrients, and also the oxygen, right? And this undeveloped part of this cell is not going to regenerate itself, because it's already undeveloped to begin with.

So it's going to go through a [INAUDIBLE]. If you look at these where the stars are, these are very hypoxic regions because of the blood supply has been cut off. So eventually, the tumor cells die off. Whereas in a normal cell, again, you're going in with this fine knife and you're cutting off certain parts. But the vasculature is so developed it could reroute itself, OK? It could repair itself, and it can supply all the nutrients.

So that's why the normal tissue could withstand much more radiation in terms of minibeam as compared to tumor cells. So here's a study that was done. If you look at the vasculature for a tumor and also normal tissue, and if we just normalize everything to be one, OK? Now after microbeam radiation therapy for tumor and also for the normal tissue, what you can see is the vasculature decreased tremendously for a tumor as compared to normal tissue. That in turn shows that the normal tissue were able to repair their vasculature and able to survive.

Here's another study. What they did was that they implanted these mice-- mice are the target for everything. So they implanted these mice with this gliosarcoma on their back. And they watched how much the tumor grew over time. And you could see the tumor volume increased over time without any type of treatment, whereas with a microbeam radiation therapy-- again, these are very high grade tumors, OK? They grow very fast. With the microbeam radiation, they were able to actually control the tumor.

And here, we look at the survival curve. With no therapy at all, the survival dropped out pretty fast. With the microbeam, they-- it fared a little bit better. So what are the requirements for microbeam radiation therapy? You need a very high dose rate-- about 100 gray per second against such as FLASH radiation therapy. And you need to make sure that you don't have any dose smearing. That's why protons are very important, because imagine when you have high dose peak and low dose valleys, you can't have any dose smearing in those areas. Because if you have that, then you lose that effect.

So that's why protons are coming up in the future. And right now, even the proton machines, even the probeam, or even the [INAUDIBLE] ones, they are becoming FLASH ready, because of these advances in technologies. And also, the high peak to valley dose is also very, very important. So you need to maintain high dose to the target while avoiding reaching dose limit to the OAR-- to the valley dose.

Again, proton-- with the proton minibeams, you could reduce the lateral scatter. Here's an example of a proton minibeam. So most-- and it could produce more distinctive peak to valley doses, and it also spares proximal tissue. Dr. [INAUDIBLE] talked about the Bragg peak. So you could deliver precise radiation with a Bragg peak. And also, protons-- you could produce a very high dose rate, as compared to other modalities.

So microbeam radiation preferentially affects tumors. It spares normal tissue. Resistance of major blood vessels to microwave radiation, which I just talked about earlier. For the tumor, it damages immature tumor vessels and it cannot repair the damage, because the supply is limited. It decreases the number of vessels. Decrease in perfusion in turn causes hypoxia, then in turn causes cell death.

So now let's turn gears. Now let's-- for a while, let's not talk about radiation therapy. So I'm going to talk about some advances in cancer therapy in general. So let's talk about nano robots. What is nanotechnology? Here we are talking about technology which is about 10 to the minus 9 meters-- one billionth of a meter. So if we take a normal human hair, that's about 100,000 nanometers. So you could imagine how small these technologies are.

OK. So these nano technologies are designed at a very nanoscale, OK? And this is made possible with improvements in microscopy, chemistry, physics, and computer science. So with the cancer, currently they are being treated with either surgery, chemotherapy, or radiation therapy, or even combination of both, correct? But these treatments-- even surgery has side effects. So imagine if you could create nanoparticles that could specifically target tumor cells. That's where the research is going right now.

So these bots, they could go and preferentially target the tumor cells, and just kill the tumor cells alone. So you're eliminating the normal tissue complication. So here's one of the research that has been going on at UPenn and also in China. So what they're trying to do is that they're trying to create these nanobots that are specifically-- and they are attaching these nanobots-- you'll see a video in a couple of minutes that will show you in detail what this is all about.

So these nanobots, they specifically have some proteins and some markers in them that specifically targets the tumor cells. Once they see the tumor cells, they go in and cut off their blood supply. They will produce thrombosis. So eventually, tumor will become hypoxic and they will die, OK? So nanobots are little devices the size of a red blood cell. And nanobots protects that thrombin, which is a protease that actually causes the thrombosis. It will protect the thrombin until it reaches the tumor cell, and detect the tumor cell, and it releases thrombin. Then that will, in turn, will clog the blood supply to the tumor cells.

So here's what they were doing. So they took some DNA from bacterial DNAs. They are called M13 DNA. And they made a mesh out of those DNAs. And this mesh is called an origami, OK? And they loaded these origamis with thrombin. So again, thrombins are the protease that actually clogs your blood vessels, right? So they'll loaded these DNA vessels with these thrombins. And they also attached these targeting molecules.

So these targeting molecules are essential to detect your tumors-- any solid tumors. Then they package [INAUDIBLE]. You roll them up, and that becomes your DNA robots, OK? So they could then-- you release them in your blood stream. They'll go and detect the tumors, and they will clog the blood vessels. So to give myself a little break, I'm going to put on a video, OK? OK. That will explain-- she will explain to me to you much more clearly about the nanobots. Hopefully it works.

[VIDEO PLAYBACK]

- Can you imagine a story where to stop a villain, the hero sends out an army of small creatures to search and destroy? Well, maybe not bugs. That's too much like a bad guy. How about fairies? No, that's too soft. It's like a bunch of Tinker Bells. I know, robots.

OK we might be sounding a little off the deep end, but something could be coming that's pretty close to what we just tried to imagine. Scientists have recently successfully shown that tiny autonomous bots have the potential to function as intelligent delivery vehicles to seek out and destroy cancer. These nanobots are made of DNA and are only nanometers in size. 50,000 of them would fit across the diameter of a human hair.

Their task is to seek out cancerous tumors and inject them with drugs that can cut off their blood supply, shriveling them up and killing them. To do this, researchers created what they call a DNA origami-- a process where DNA is folded into specific shapes. In this case, the DNA-based nano robot was formed into a hollow tube carrying the blood clotting enzyme. Each strand of DNA keeping the tube closed is designed to detect a specific target, like a protein linked with cancer.

If the DNA strands detect their respective protein, they untie and the tube opens, allowing the bot to deliver its payload directly at the cancer. The technology is modeled after our body's own defenses. Like white blood cells, the nanobots patrol the bloodstream looking for signs of distress. DNA is a naturally bio-compatible and biodegradable material, and the devices are designed to not incite an immune response.

The scientists behind the study tested the delivery bots by injecting them into mice with human cancer tumors. Within 48 hours, the bots had successfully grabbed onto vascular cells at the tumor sites, causing blood clots in the tumor's vessels and cutting off their blood supply, leading to their death. Remarkably, the bots did not cause clotting in other parts of the body, just affecting the cancer cells they'd been programmed to target.

The molecular programmed nanobots can be directly injected by syringe with up to 1 trillion nanobots to seek out and perform cellular tasks by means of molecular sensing techniques. The possibilities of this technology are endless and extend beyond the killing of cancer cells. Some functions could include delivering enzymes to break cells down via programmable nanoparticles or delivering insulin to specific sites.

Currently, the nanobots can identify 12 different types of cancerous tumors. Researchers also envision the possibility of using this tool in seemingly healthy people to screen the body for any type of cancer before it can spread. Clinical trials in humans are expected to follow, and it is hoped that the results may have the potential to save millions of lives. Well that's all the time that we have the time for. Tune in next week if you want to see more.

[END PLAYBACK]

LALITH K. KUMARASWARMY: OK. Good. How's that video? Good. Good.

AUDIENCE: [INAUDIBLE]

LALITH K. KUMARASWARMY: Because they are made up of DNA, anyway. So they get secreted out. So once they release their payload, they become part of you, or they get released out. That's why she was saying it doesn't cause any negative side effects.

AUDIENCE: [INAUDIBLE]

LALITH K. KUMARASWARMY: Yes. Yes it does. But there's a lot of research still needs to be done. These are very in infancy stages. I mean, it works for several tumors, for several patients, but not everybody is benefited from that. There's a lot of research has to be done.

So here, again, there is a mouse model. What they did was that they implanted these mouse with tumors. And they injected these mouse with nanobots without any payload-- that means without any thrombin. So thrombin is very key, because that's the one that clogs your blood vessels. And they also implanted some dummy markers. And what they were found was that nanobots with thrombin inserted, it was able to control-- actually, it will decrease the tumor volume, as compared to the other empty [INAUDIBLE], OK? So you can see the potential here. Even if you look at the survival curve, nanobots with thrombin-- with the correct payload-- the survival curve-- survival of these mouse was dramatically increased.

So let's talk about-- now I'm going to switch gears again, coming back a little bit to radiation therapy. But I'm going to talk-- first, I'm going to talk about immunotherapy and how radiation and immunotherapy can be combined to be more optimal. So to understand immunotherapy, we need to understand our immune system. So our immune system is made up of two immunity. One is called innate immunity. Those are your dendritic cells, macrophages, your neutrophils.

These respond-- they don't respond specifically, OK? So if a foreign invader comes into your body, they respond right away. They don't distinguish. OK, am I-- do I know this virus or bacteria? They respond right away, OK? But they don't have any memory. So if the same foreign invader comes the next time, they won't remember, OK, this is the same guy or same response I should have the previous time. Whereas an adaptive immunity, such as B cell or your T cells, they are pathogen and antigen specific. So they don't respond to everything that invades. They have to be specific, OK? That's why they take time to respond.

And exposure-- even if the pathogen comes back later on, they will remember. And they will attack them right away. Those are your adaptive immunity. So let's talk about it in a perfect world, how your immune system could attack cancer. It doesn't happen, but let's say how would-- in a perfect world, how it would happen. So you have a tumor here. Tumor will release antigens, OK?

These antigens get picked up by your dendritic cells, right? Those are part of the immune system. They get picked up by the dendritic cells. Then they present these antigens-- the dendritic cells-- to your T cells, OK? T cells are the one that your-- killer B cells, killer T cells. They're the one who goes and kills your tumor. So they present this to your T cells. Then the T cells have to get into your bloodstream with that information-- with that antigen information in their hand.

Then they'll get into the bloodstream. Then they'll go to the tumor site. They'll seek out where your tumors are. They'll go to the tumor site. Then they have to get inside-- get access to your tumor. They have to cross a barrier. Once they cross a barrier, then they positively detect your tumors. Then eventually, tumor cell death, OK? That's your basic-- in a perfect world, that's what happen.

But that's not what happens. Your tumor has a lot of defensive mechanism. It promotes a lot of inhibitory factors along the tumor surface, such as anything that is in the red, those inhibit your T cell activity. Or anything along this pathway, it inhibits those activity, right? So here, for example, this CTLA4, it inhibits this process, whereas these green, they positively-- they actually promote this process. But eventually-- so there has to be a balance between these green promoters and these red promoters. But eventually, these red promoters win out.

So that's why there's a proliferation of cancer cells. So if you-- let's just look at some of these properties in detail for a second. So in a normal cell, typically you have this activated T cell. They go in turn and will attach, positively identify a normal tumor cell. And they'll attach it to a tumor cell. And they will eventually kill it, or it will make it go through apoptosis. But there are several ways that cancer could evade that.

One of the ways is that it could form an anatomical barrier between itself and the T cells, which is coming to create the damage. So one of the processes is creating an anatomical barrier so the T cells can't penetrate. Second option is that these tumor cells could present what is called FAS ligand, OK? So once that is presented on the tumor cells, when the T cells comes and attaches to the tumor cells, these FAS ligand, they actually promote the T cells to go apoptosis. So instead of tumor cells going apoptosis, they actually-- the T cells will die off.

That's one of the defensive mechanism. Another one is that there's another molecule called CD152 that tumor present, where it actually inhibits the T cells function. And there is another option also that the tumor has, which actually inactivates your T cells. So those are the possible ways that tumor could protect itself from your immune system.

So how does radiation and immunotherapy work together? So if you want to kill a tumor cell, there's two things have to happen. You need to induce a tumor cell to release a tumor specific antigen. Remember the antigens that I talked about. These are the antigens that tumor cells releases, and the macrophages and the T cells recognizes that. And they can go and destroy. First of all, we need to make sure that tumor cells-- we need to somehow make-- induce the tumor to release these antigens.

Second is that we need to suppress all these markers that are on the tumors so that when the T cells eventually come, they won't inactivate those T cells, OK? So those are the two key things that need to happen. So these markers-- the CTLA-4 and this PD-L1, they down regulate your T cell, OK? That's what I just talked about right now.

When you give radiation, two things happen. First, radiation increases the expression of the death receptor called MHC 1. And this MHC 1 promotes the release of tumor antigens, which is good, because you want the tumor to release these antigens. So when these tumor releases antigens, your dendritic cells, your macrophages will come and detect these antigens. And they could come and pick them up.

But unfortunately, radiation also has an immunosuppressive effect, because it also promotes the expression of further markers along the tumor cells, OK? What that does is that these markers-- for example, this PD-L1, it promotes inactivation of this MHC 1. So now, the dendritic cell cannot detect these antigens anymore, OK? That's where the immunotherapy comes in. So immunotherapy, what you could do is that you could deliver these anti CTLA-4 or PD-L1 drugs to suppress these markers around the tumor cells, OK?

So once you suppress these markers, now this MHC could correctly transfer this antigen into your into dendritic cells. Then, your T cells could recognize these antigens. Then what happens? Then T cells could go in and kill those tumor cells. It not only kills the tumor cells which are irradiated, but also affects the tumor cells which are in addition metastatic, as well-- a non-radiated metastatic cell-- tumor cell.

So that effect, as some of you know, it's is called the abscopal effect, where you don't have to radiate the entire tumor. But if you radiate part of the tumor, you could promote tumor cell death. So abscopal effect is a phenomenon in the treatment of metastatic cancer where localized radiation treatment of a tumor causes not only a shrinkage of the treated tumor, but also the shrinkage of tumors outside the scope of the localized treatment, OK?

So that-- lot of investigation has been going on to see whether this is effective for metastatic breast cancer, colorectal cancer, lung cancer, and melanoma. So here's an example of a patient who got treated of three lines of chemo and radiation therapy and didn't do anything. I mean, the patient progressed. So you can see here your multiple mets-- even the lung and also in the liver.

Then this patient received immunotherapy with radiation. So he was deliver an SPRT treatment of 6 gray times 5 in combination with immunotherapy. And they just deliver radiation therapy one of the liver mets, OK, even though this patient had multiple mets. So look what happened after about six months. The scan showed even the mets outside of the radiation field disappeared after about six months.

This is the abscopal effect, OK? But again, this is fairly-- in the beginning stages of investigation. There's a lot of work needs to be done to improve this combined technology. I'm running out of time. I'll just go through this very quickly. So there is another example with multiple metastatic patient. What they did was that they delivered radiation at this point. So he has multiple mets at here, here, and also at this region.

So they deliver radiation for this target here with a combination of immunotherapy. So after several months of monitoring this patient, they were able to see that all of the tumors were started shrinking. So there's a lot of other studies who are also going on right now. Again, these are all in very beginning stages of the study.

So what are the advantages of RT based cancer immunotherapy? Well, it specifically targets and limits collateral damage, OK? Because it's very specific, because we are specifically targeting with your immune system the specific target. And the target is non-dissectable tumors. So even when you have a non-dessictable tumor, you could treat for this technology.

And T cells can target tumors at sites throughout the body. So as I said before, T cells remembers, right? So even if the cancer comes back-- same type of cancer comes back later on, T cells has a memory to go back and destroy it. So you don't have to treat the patient again. So it has that memory. So it provides long lasting protection.

But still, many questions remain. What are the optimal sites to radiate a metastatic disease? Patient selection. Sequence of-- what is the best sequence of radiation therapy as compared to immunotherapy? And we have to figure out what the optimal radiation dose in combination with fractionation, and also the best combination.

So as a summary, very quickly, preclinical and clinical evidence suggests that local radiotherapy can contribute to the efficacy of cancer immunotherapy by rendering the radiated tumor more immunogenic. Radiotherapy can be harnessed as an adjuvant or immunotherapy as it may convert non-responding patients, as we saw before, to responding to same immunotherapy, OK? But the dose fractionation and sequence of radiotherapy need to be explored in combination with immunotherapies strategies.

So here's one of the questions. It's my last question. So what are the mechanism of tumor escape from immune response? One, target cells down regulate the proteins responsible for presenting the tumor antigens to the immune system. There's an anatomical barrier preventing T cells from reaching the target cell. The target cell can use a FAS ligand to promote T cell apoptosis, or regulatory T cells could send false messages to the killer T cells, preventing the T cells from killing the target cells, or five is all of the above. 5. 5. OK. Go ahead.

Whoa. Look at that. OK. Everybody got it right. All of the above. With that said, thank you. That's all I have today.