Biophotonics
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Lecture 38
Light Irradiation for Photodynamic Therapy (PDT)

Welcome back, we are discussing about Photodynamic Therapy, light-based therapy in which drugs gets attached to specific cell specific abnormal cells that we want to destroy and these drugs upon activation by light produces reactive oxygen species mostly and these oxygenated species oxidizes the cell to which they are attached to thereby destroying the abnormal. That is the overall idea. Now, let us discuss a little bit about the light that we are sending.

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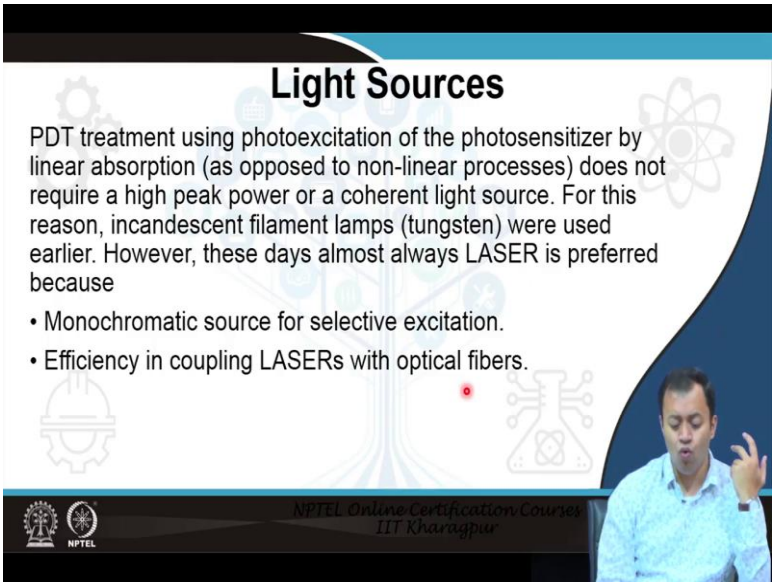

Now, this needs to be accepted that firstly, it is a linear process, there is nothing nonlinear about it. So, it is a linear absorption, more light you send the more light gets absorbed and it is a linear process going on and we do not have a mostly nonlinear areas inside our body.

There are exceptions, collagen is a primary exception, but overall it is a photosensitizer the excitement of photosensitizer usually follow a linear absorption pattern and it does not require a high peak power or coherent light source, anything, if the drug is sensitive enough and if you have shown light on to it, especially in your skin treatment, when you are doing PDT in your skin, a lamp of correct wavelength can perform PDT.

You do not require a very high peak power or coherent light source. A lamp can work or if you remember porphyrin or hematoporphyrin drug, they are special people who injected

them, they were specifically asked to stay away from strong light or sunlight, they have to stay indoors in a dark condition for four to six weeks. Because the drug was still available still retained in their body it takes a long time to get discharged, get excreted out and they may cause damage.

So overall, it is the sensitivity of the drug for a particular wavelength and since it is more or less a linear absorption process, especially if the drug is applied externally to your skin, then you do not require laser light source. However, we use laser simply because it is monochromatic or it has a very selective wavelength

Thereby it can be selectively targeted and most importantly, lasers are targeted with optical fibres and with the optical fibre what you are doing, you are not only delivering the light, you can make two or three optical fibre simultaneously together and put it near the area and thereby extract some reflected light some back scattered light and analyse it to see what exactly is going on.

Meaning you can monitor the entire process of photodynamic therapy at real time. You know these optical biopsies happening there are more than one fibre, one fibre is sending a specific amount of light and the light is after hitting the tissue is getting extracted, the extracted light is you know taken back by another fibre nearby and that light is analysed and you get information about the properties of the area that light is hitting. So, why cannot we do this here?

Why cannot we do this here, there are a bunch of optical fibres that are combined together in very, very thin tubes few micrometres in diameter, the entire thing is less than few millimetres in diameter and it is put inside some sort of through either a keyhole surgery or something through an orifice and then one of them contain the specific laser light that excite the photosensitizer drug and rest of them are simply monitoring.

The rest of them are simply collecting the light and monitoring what is going on, monitoring the surrounding area, thereby you are overall monitoring the PDT process. Therefore, for all intent and purpose instead of shining torch light in your mouth. We use lasers and optical fibres.

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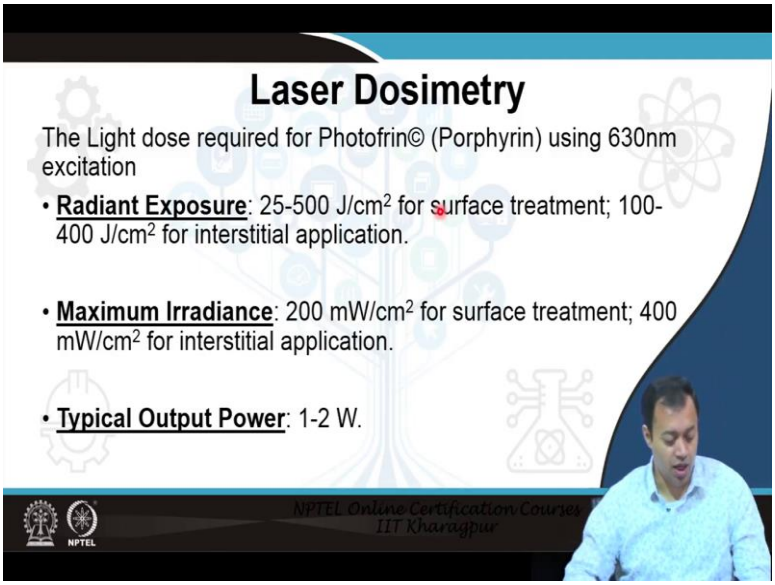

So, this is a very real-life example for this porphyrin. So, photofrin is the copyrighted name of that drug the company sells. Porphyrin is the obviously the compound and which is the light sensitive photosensitizer and these are the light dose this is the real lab. So, I actually got it from reliable sources from NHS.

I think and this uses 630 nanometre excitations, since this was the oldest one all information regarding porphyrin is available over the internet you can simply access it several of the other photosensitizer drugs are copyrighted, I am therefore putting the copyright things, so that there should not be any infringement afterwards.

Several of these newer forms of drugs the entire details are restricted and not for public use mostly health professionals know them anyways. So, these are the actual doses that you do. So, if you are going for a surface treatment surface treatment means outside the surface and interstitial application means when it is inside somewhere the cancer or the targeted cell is inside the tissue.

So, these are the exposure that you can do 25 to 500 joules per centimetre square for surface treatment whereas 100 to 400 joule per centimetre square for interstitial application. I think it is self-evident right that why the energy per centimetre square is less, when it is surface treatment, but more when it is interstitial application.

If it is not clear, then I asked you to discuss this and come up with an answer, I will not be giving you all the answers and this is pretty straightforward why you require more energy when you are sending light inside a human body.

Maximum irradiance 200 milli watts per centimetre square for surface treatment 400 milli watt for per centimetre squared for interstitial application and the major problem that we are facing in PDT is the output power has to be 1 to 2 what remember in previous one of the lectures when I encouraged medical practitioners or biotechnologists or even nanotechnologies to try to utilize this in your lab, some kind of a petri dish.

The biggest deal breaker happened to be apart from the drug of the cost of the drug is 1 to 2-watt laser though this is not impossible to get and several well-funded laboratories do contain lasers which has 1 to 2 watt or even higher wattage, but 1 to 2 what is not exactly the power that you get out of a normal laser pointer.

So, you have to have a slightly more effort you have to show more effort to actually do the experiment. So, this is the overall protocol, the protocol already exists for porphyrin and different types of drugs are being generated, which has similar dosimetry, dosimetry is basically the dosage.

Pharmaceutical students know it pretty well what dosimetry is and they are asked to calculate I know I have seen some of their syllabus and dosimetry is probably one of their specific subject specific paper. So, this is the dosimetry for porphyrin drug for PDT. So, all of these exist, all of these exist and you obviously get dosimetry or you obviously optimized dosimetry when it has been standardized or when it has gone through lots of trials and tribulations.

So, this actually exists. Rest of the time, I am actually encouraging you to develop your own dosimetry by working on first petri dish and then move on from there to a mouse maybe and then finally, do preclinical studies and then go forward to treat actual human beings.

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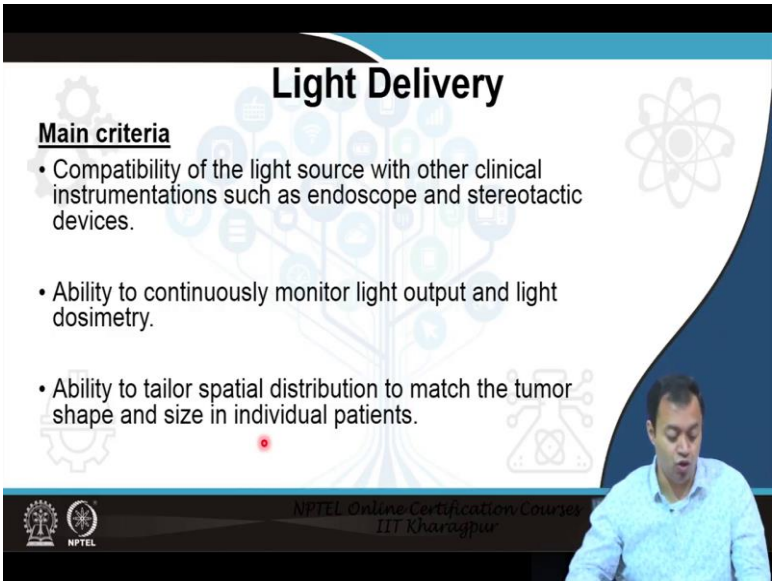

So, how do you deliver the light? Well, the compatibility of the light source with other clinical instruments such as endoscope and stereotactic devices, we need to, so thereby one of the main reasons why we utilized optical fibre is because we wanted to connect an endoscope with it, so that we could monitor the environment.

How in real time if we can monitor the tumor destroyed the tumor getting burned the tumor getting oxidized. We have an endoscope and optical fibre connected with either relay lenses or these days camera to actually see monitor the tumor in real time and how much more drug you need to do how much more intensity of light you need to produce, you can actually get a good look, we can actually monitor the entire experiment in real time and we can see.

So, the light delivery has to be something that is compatible with other diseases that makes all of our life easy. It is waste, you have to simply wait X amount of time and think that the tumor has simply reduced, the tumor has simply oxidized we need to monitor it as well. Yes, this is the ability to continuously monitor light output and light dosimetry this is part of endoscope, but in a more open sense, optical biopsy you are sending bunch of light and collecting bunch of light and thereby continuously not only just seeing, but understanding that chemistry change.

Some of the light that gets scattered will carry the information of the molecules that it has scattered the molecules that it has vibrated and thereby, we can understand basically the physics change as well as the chemistry change, hopefully something else not have come up

because of the burning, hopefully healthy cells are not being burned and we need to tailor the spatial distribution to match the tumor shape and size.

So, this is your tumor and this is your light, how much of it is getting destroyed, is it just this part or it is the entire region. So, you have drug here and you have drug all over this place, but say your light is only inducing this biochemical reaction here, will it be enough to destroy the entire thing or it will partially destroy the tumor or the light will not since light is not able to go in the back corners, the back alleys, this part remain intact.

So, those are basically the dosimetry that needs to be calculated that needs to be optimized and thereby, what sort of light that you need to send, what wavelength, how much penetration depth it has on the specific tissue all of that needs to be measured. Remember the course on the module on interaction of laser with biological material; I give you a chart of which laser penetrates how far in which specific tissue.

So, utilize that chart and try to see and that chart will be helpful in determining basically, what sort of wavelength of laser that you need to send at what intensity what power density et cetera, to destroy either different types of tumors or same tumor of different size, one is small, one is big the same tumor, same type of tumor small and big, all different types of tumors.

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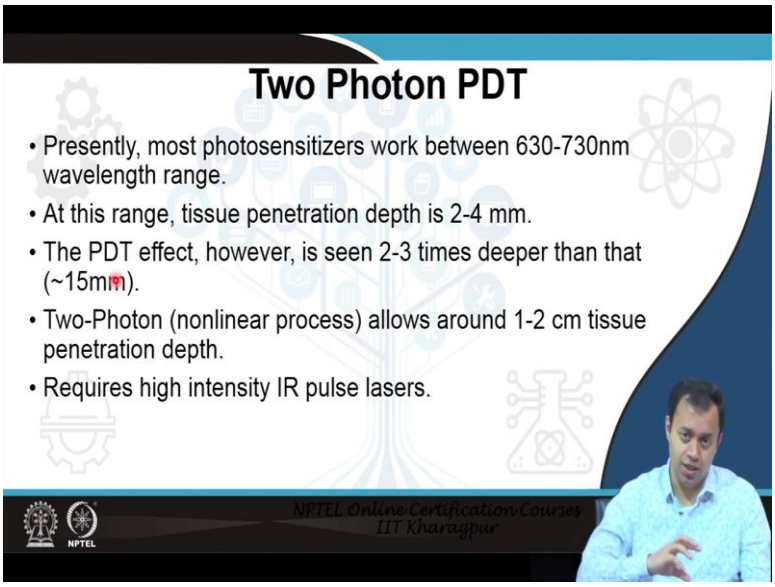

So, these days, we are mostly looking into non-linearity to photon PDT. So, most photosensitizer works in 630 to 730 nanometre wavelength range. Remember, this is not

exactly the window where they will the biological tissues are transparent, biological tissues are more or less transparent, well by transparent I mean the scattering is comparatively less from I think 630 to 1350 nanometres.

So, you have an entire range, where the tissue is scattering less, so more amount of light could be penetrated. So, most of the photosensitizer work at this range and here most of the laser penetration is 2 to 4 millimetres, you can increase the power of your laser, you can increase the intensity of your laser, thereby increasing the depth but that might generate heat in the surrounding areas thereby destroy healthy tissues. So, it basically defeats the purpose.

So, the optimal energy of light, optimal intensity that presently is working only allows it to go up to a depth of 2 to 4 millimetre and that is pretty small. So, if you have a very, very internally born tumor, something inside head and you need to excite it, your drug will go and attach to it No problem. You have some sort of an antibody antigen complex something you have formed. But, how to excite it?

If you are opening it up and then inserting the tube that far, you might go for a surgery anyways, you might go for a surgery anyways. So, that is presently the problem, presently the bottleneck is that the tissue penetration is less than 2 to 4 nanometre the PDT effect. Well, we have seen 2 to 3 times deeper than that 15 millimetre can be achieved because as I said the fibre does not necessarily need to go at the source of the tumor as long as the light that is coming out of it is able to penetrate you have used optimized light you have used into the particular frequency at 15 millimetre, but still millimetres are small, millimetres are small we need something in the range of centimetre.

If we are going for you know penetrative depth of tissues, tumors which are deeply buried, we need to go at centimetre range and that is these days developed by two photon PDT that is developed these days by two photon PDT. How do you envision two photon PDT might happen? Remember a two-photon microscopy, nonlinearity we discussed this thing in which two photons are coming and third photon is coming out two photons are coming into the input and the third photon is coming out into the output some sort of non-centrosymmetric happens.

I am asking you as an exercise, I am leaving it as an exercise to look into nonlinearity processor two photon PDT This is a very, very interesting and emerging field. I will give you all the hints that you need, you can ask me to the forum. So, overall it is a nonlinear process.

Overall you require a material which is non-centrosymmetric, i.e. which has second harmonic generation capacity, i.e. which takes two photons in the input and produces a third photon, the third photon has double the energy obviously 2 omegas plus omega gives rise to 2 omegas.

So, red lights two photons two pulses can form blue light in the laser we utilize it for tuning lasers or we send infrared light two pulses of infrared light can combine and generate frequency at visible range that has a slightly higher energy and thereby it can penetrate but you are not sending that high energy light throughout the entire process.

So, this is the area where your tumor is, this is the area where the drug is, this drug is energized by two pulses, the two pulses converts a nonlinear process the nonlinear process result in these drugs generating another photon that photon is going little bit farther to activate another photosensitizer which is then connected with your tumor.

It is a very, very new and someone asked me what are the hot topics of research, this two photon PDT is a very, very hot topic in research. We have not yet been able to optimize it There are numerous papers I know, I know and if you are researching on this regard kudos to you, but it is way too far away, way too far from standardizing or optimizing or actually showing very good results and you can use high intensity IR pulse lasers.

So, less energy light can be sent, they will enact upon photosensitizer material upon a nonlinear material that nonlinear material upon reaction of these two sets of IR pulses, because of the non-linearity process will produce a photon which is of far higher energy and that far higher energy will go further and will activate another photosensitizer which is connected with drug. So, it will allow around hopefully 1 to 2 centimetre as compared to 2 to 4 millimetre or even 15-millimetre penetration depth and thereby we can target deeply buried hidden tumors.

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So, this basically is the overall light-based photodynamic theory light sources from, I discussed light dosimetry and two photon PDT, I gave you enough hint on two photon PDT I would ask you to study a little bit more on two photon PDT it is quite an interesting topic and we will continue our discussion further on various topics of light activity therapy in subsequent classes. Thank you.