Nanobiophotonics: Touching Our Daily Life
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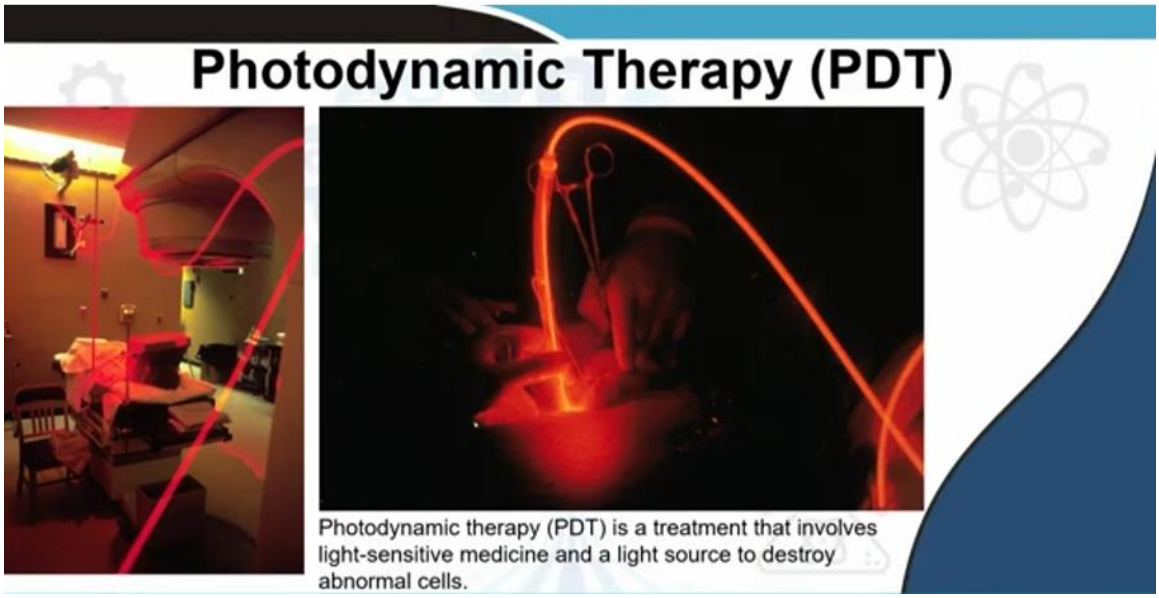
Lecture No. 34
Light/Laser Activated Therapy

Hello and welcome. We are at module number 7 that is Lasers for Biophotonics. And in the previous few lectures we have discussed what lasers are, how they can induce nonlinearity effect on certain materials, certain complex compounds. And at the same time, we have seen that how these laser lights could be delivered at different areas of the body, different lasers have different penetration depth. So, they could be very well utilized for a direct interaction of the human body, different parts of the human bodies' tissues, organs, blood vessels, nerves etcetera. They could be impinged or they could be interacted upon by different varieties of laser.

A significant way in which lasers could be utilized it not necessarily just for imaging which is very much a part, but also for therapeutics. Now remember biophotonics is not just about imaging the biological matter, then it should have been called bio imaging or just imaging for that matter. It is also containing an element of therapy that means it could also be used for cure. Today in this chapter and the next one I am going to discuss about how laser light could be utilized in human body for curing of certain elements.

So, welcome to today's chapter. Today's chapter is light or laser. Most light these days that are being used in biophotonic applications are lasers, but sometimes the exception is there. So, I have kept both and today we are going to discuss light activated therapy or laser activated therapy. Now the very first one on which we need to discuss is the photodynamic therapy.



Now this is something that is pretty recent cutting edge and lots and lots of research these days are being conducted all over the world to understand and to further refine and develop the so-called photodynamic therapy or PDT. At this present moment PDT or photodynamic therapy is fully approved by the Food and Drug Administration FDA of the United States for treatment of certain cancers meaning it is already in the market. Certain cancer is already being treated by this photodynamic therapy. So, it is not exactly in the research realm that it is going to show potential, it is going to show some sort of a probable cure in the near future. It is already been done.

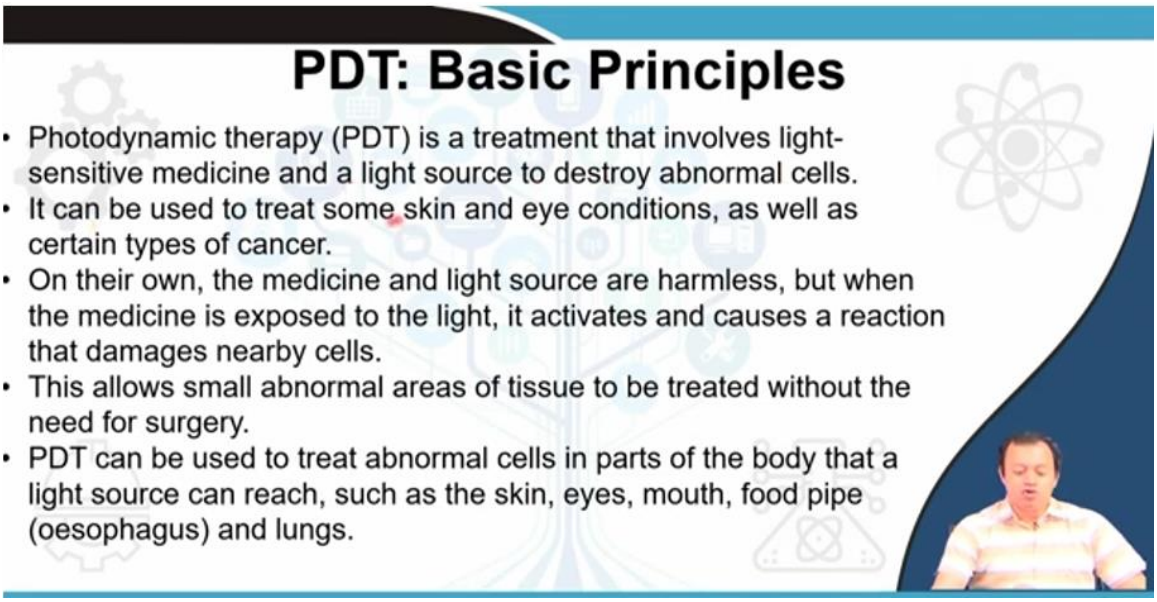
It is already been done to treat certain types of cancer especially skin cancer, especially some kind of a skin-based disease you will immediately see why. The idea here is to expand its scope. The idea here is to expand its scope and take it to a far different variety of ailments diseases that could be treated with photodynamic therapy. So, what is photodynamic therapy? Is a treatment that involves light sensitive medicine, light sensitive medicine and a light source to destroy abnormal cells. You need a medicine that reacts that changes its property when it interacts with light, not just any light a specific frequency, a specific wavelength, a specific energy of light and an obviously, a light source.

A light source is delivered towards the medicine. The light is made to go towards the medicine and excited the medicine then starts its work. So, this is the very interesting image. These are the optical fibers. We discussed about optical fibers.

This is the patient's bed and some sort of perforation or a hole is being made inside patient's body where this optical fiber is being dealt. You see seizures the surgeon has actually made a hole made an incision a cavity inside the human body inside the patient's body and then this optical fiber tube is inserted which contains light which contains red

light, reddish orange light which is then being made to excite a particular area inside the body perhaps an organ which contains some amount of this light sensitive medicine. You absolutely absolutely need a light sensitive medicine, a medicine that will react only only when this particular wavelength of light is exciting it. Nothing else will work. That is how you get sensitivity.

So, this overall process in which a light sensitive medicine which is already pre-inserted into the body and a light source then exciting it and then it starts its work is photo dynamic therapy. Photo is light dynamic you know continuously rapidly evolving rapidly changing therapy is therapy. So, what are the basic principle of PDT?

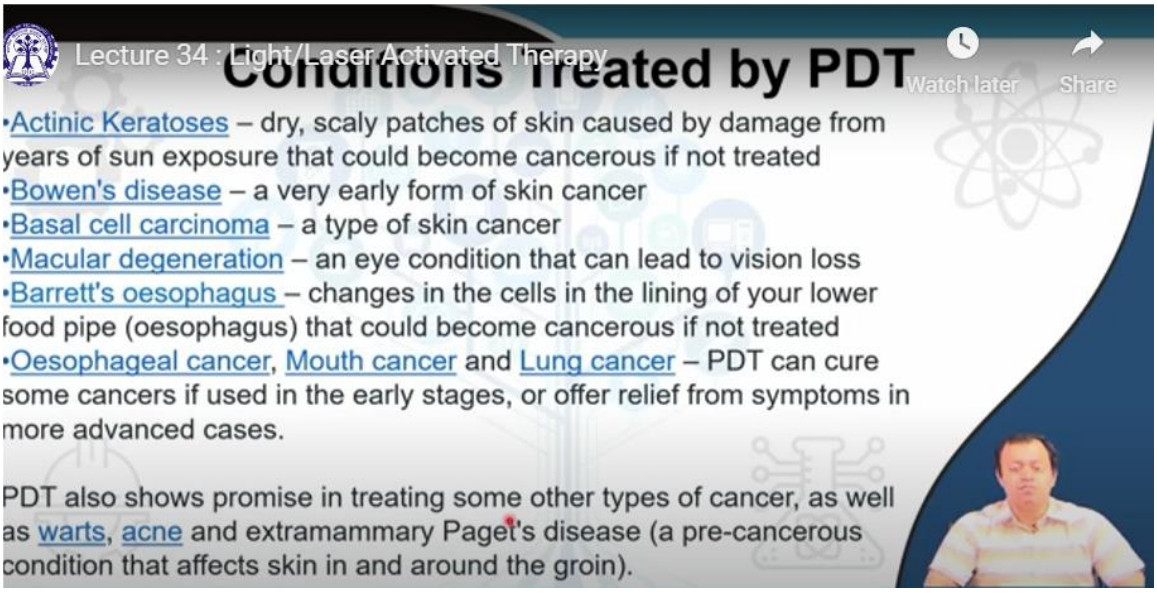


Dynamic therapy is a treatment that as I said that involves light sensitive medicine and a light source to destroy the abnormal cells. It can be used to treat some skin and eye conditions as well as certain types of cancer. Now here is the important part on their own the medicine and the light source are completely harmless well let us not use the term completely they are more or less harmless.

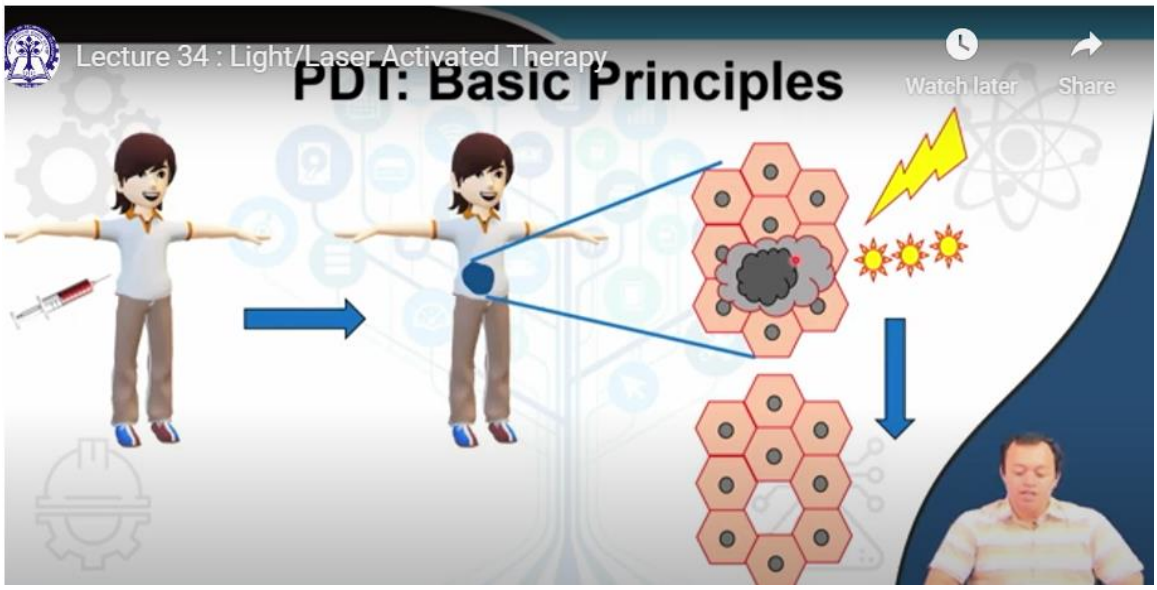
The medicine and the light source are harmless, but only when the medicine is exposed to a light it activates and causes a reaction that damages nearby cell. So, you need two things light sensitive material and light. Just by itself the light is more or less harmless just by itself the medicine is more or less harmless and has no effect. Combine these two combine these two this medicine starts working it starts some sort of a chain reaction and the overall output or overall goal of this chain reaction is to damage the nearby cells is to damage in this particular case abnormal cells. This allows small abnormal areas of the tissues to be treated without a need for surgery and PDT can be used to treat abnormal cells in parts of the body that a light source can reach you have to have a light source

reaching that area and thereby I said skin and eye outer surfaces mouth food pipe are very easy to treat with photodynamic therapy.

You need a light source to go there yes I have shown you the previous picture in which a hole is being made an operation has been made and then you are sending light source, but understand that contains risk that contains huge amount of complications instead of that it is much easier to put that medicine on your skin and then shine light of in from outside and thereby take care of it such as skin cancer, eye problems, mouth food pipe and lungs where there is already a pre existing cavity and some sort of optical fiber could be inserted inside. So, what are the conditions what are the types of disease that are treated by PDT what is PDT capable of well several first and foremost the skin dry scaly patches of skin caused by damage from years of sun exposure.



So, several types of skin based in men not just cancer not just skin cancer, but different patches warts your acne's some kind of fungal infection on skin I will show you images at the end. Then bones diseases early form of skin cancer different types of skin cancer macular degeneration the eye condition that leads to vision loss glucoma oesophagus mouth cancer lung cancer and as I said warts or acne I think I pronounce it wrong I call it rats its warts or something like that acne several of these diseases several of these diseases can be treated using photodynamic therapy.



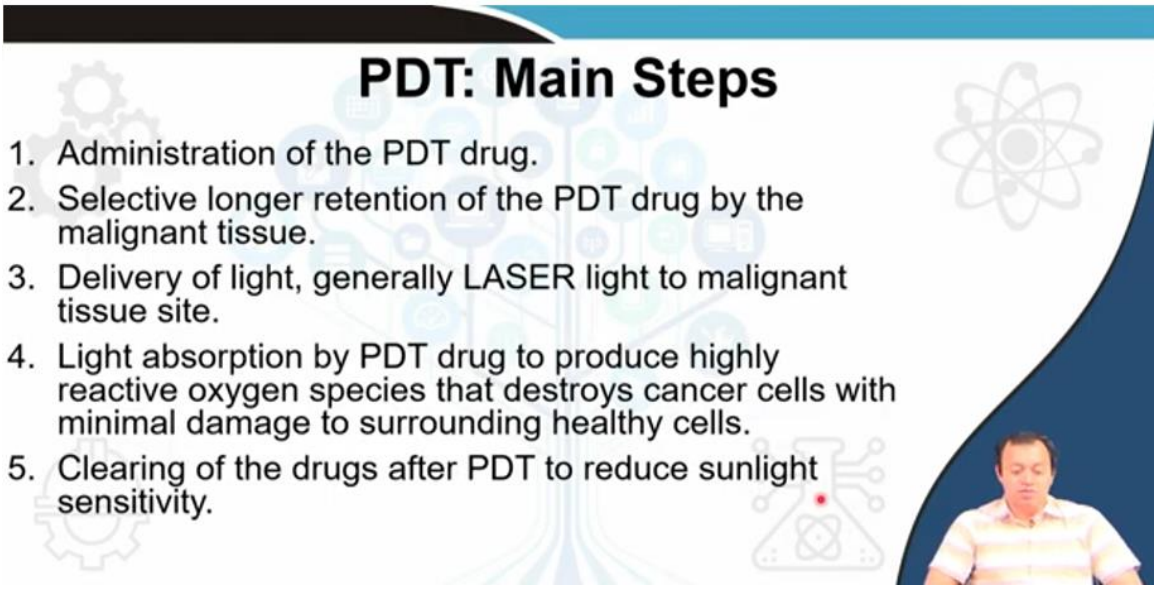
So, what exactly is the basic principle of photodynamic therapy a patient comes a patient is injected with a particular drug the photosensitive drug the photosensitive drug at the beginning at the beginning gets distributed all over the body get distributed all over the body the abnormal cells as well as the normal cells both then you have to wait after certain time after certain time 2 hours 3 hours 2 days 3 days the drug the medicine will accumulate specifically to the abnormal cellular areas right.

You will have to wait for the drug to concentrate to coagulate on to the areas which are abnormal I told you several times this could be done using antigen antibody kind of reactions where a specific protein attaches to any specific protein. So, abnormal areas abnormal cancerous cells have their own proteinous distribution different amounts. So, that could be done at the same time some aptamer base sensing aptamers are small molecules small molecular chains of proteins that could also be utilized. So, there are several ways in which selectivity could be achieved. So, in the beginning in the beginning the drug get administered into the body and it distributes throughout throughout the body, but it could only attached covalently nicely with certain specific condition that it has been fixed with rest of the areas rest of the areas of the body where it has accumulated either it failed to bond or after bonding or certain time it is either renally discharge or it does not remain in that particular places.

Obviously, that is the ideal case some amount of normal cells are obviously, also affected, but this drug then get affected then get accumulated then get impinged then get concentrated on to specific area of the body which has been targeted because of it abnormal cellular chemistry yeah cancer cell have a different chemistry than normal cell. So, we understand what kind of cancerous cells what kind of chemicals are present in that cancerous cell we try to design our drug to get attracted towards that specific specific

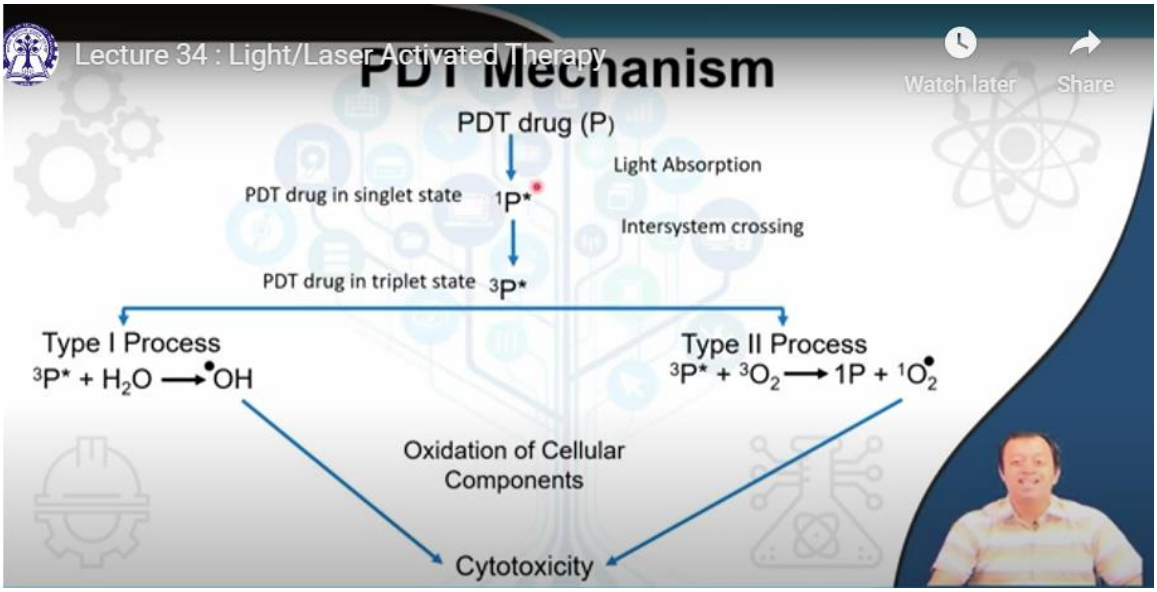
chemistry. We create covalent bond materials that attach with that particular abnormal chemical region cellular chemical region and after certain time after certain time it is like when your mix some kind of a salt or sugar on to solution and then wait for the solution to precipitate and localize into certain areas of the beaker quite similarly the drug needs to be given time. So, that maximum amount gets precipitated into the abnormal region and tiny bit still remains into other regions it is then activated. So, this is the area this is the cell and this part of the cell is the bad cell the cancerous cell your drug will be injected in this particular area and then you excite light on to it the light will cause this chain reaction which is inside the into the drug resulting in the damage complete cellular damage that area of the cell is burnt literally it is oxidized it is burnt it is evaporated it is melted the beauty of the thing is it is more or less selective very few amount of drug is in the normal area almost all of the drug is accumulated on to the abnormal area this abnormal area is excited with light the drug then causes the abnormal cell in which it has been injected to burn to melt to evaporate.

Since there are no drugs or very very little amount of drug in the surrounding cellular region they are either not affected or minimally affected whereas, the cancerous part the abnormal part is simply evaporated without causing much harm to the surrounding area. So, this is the basic principles of photodynamic therapy.



So, the main steps are simply we administered the PDG drug the selective longer retention of the PDG drug by the malignant tissue malignant or the cancerous tissue has a longer retention delivery of light generally laser light to the malignant tissue site light absorption by PDG drug. So, now, what exactly does the drug do after absorption of light? Well the best thing or the fundamental thing that PDG does is it creates highly reactive oxygen species ROS reactive oxygen species these are radical's oxygen radicals remember what

radicals are from your high school chemistry radical of oxygen and they destroy the cancer cell with minimal damage to the surrounding healthy area. Once this process is done the remaining drug whichever has not been converted into reactive oxygen species are simply renally discharged it is discharged from your body through urine or feces after certain time ok.



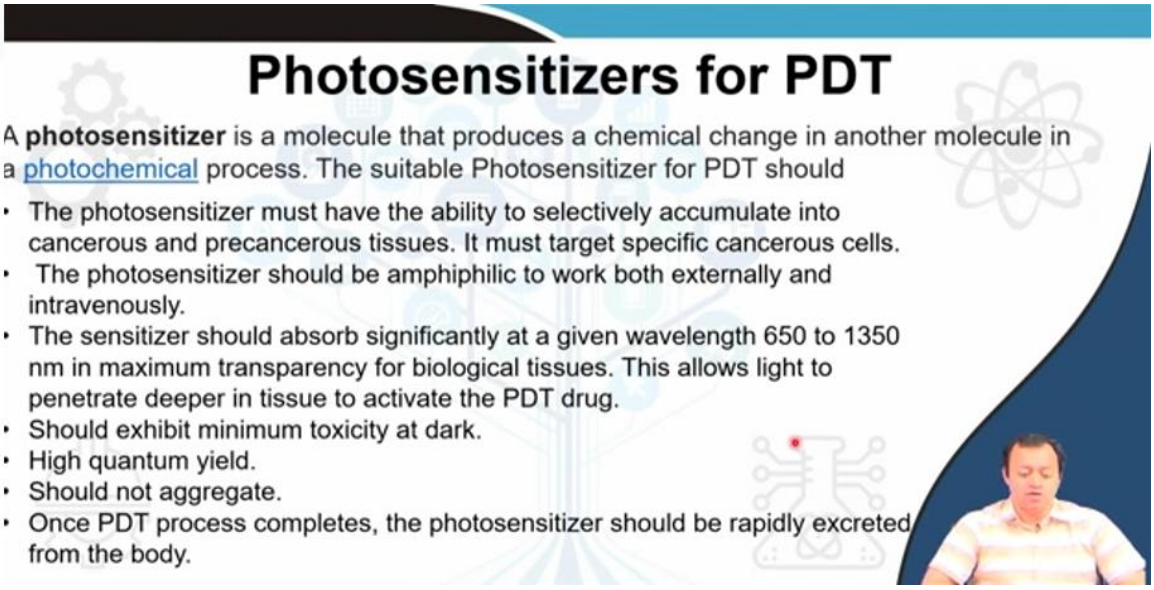
So, what exactly is that ROS generation reactive oxygen species generation? So, the idea here is that you create some sort of a drug complex complicated molecule you know pharmacy or any kind of drugs or medicines are complex molecules and when it is injected and when there is a light excitation a particular wavelength of light is being brought in very very close contact to basically excite the drug with light there is a singlet state remember your fluorescence class the singlet state S 1 the pharmacy people use P 1 I do not know why, but exactly the same thing S 1 is P 1 star it creates a singlet state you know the electron has moved from lower level to upper level it has moved from lower level to upper level and the spin is paired the spin is paired in in in this direction it creates a singlet state. After sometime the electron moves into a defect state by interstate intersystem crossing it has moved to a quantum defect state you create your molecule you create your drug. So, that it has this defect you create your drug. So, the drugs medicine. So, that the intersystem crossing is available when the intersystem crossing happens you know the spin is unpaired the spin is unpaired and this is the triplet state the T 1 state again pharmacy people call it 3 P I think this is actually better 1 means singlet 3 mean triplet star means those excited states no star means ground state.

So, from 1 P to 3 P triplet states triplet states are the one which is phosphorus this is fluorescence this is phosphorescence this phosphorescence. So, there stay there for a longer period of time remember phosphorescence stay there for a longer period of time it slowly slowly emits light it goes on forever unlike fluorescence which is there for 10 to the power 10 nanosecond or so, it returns back. So, what happened is this triplet electron

this triplet electron this triplet state of the electron combine with either the water molecule present near that cellular area present near the cancer cell water and oxygen are the 2 most abundant compound water and oxygen are the 2 most abundant compound in human body several one of the most abundant compound 2 most abundant compound and this free electron or this more or less stable electron this triplet electron reacts with the the water creates a hydroxyl group creates a free radical hydroxyl group or it creates a free oxygen radical species either hydroxide or dioxygen, but both of them this dot is the symbol of radical radicals are very highly reactive chemical species this extra electron this extra electron either knocks out one of these hydrogen and creates a hydroxide this is highly unstable it needs to attack something to get a hydrogen is present in somewhere else it needs to take it from that part similarly there is an extra electron present in this free radical oxygen. So, both of them try to take it by oxidizing by burning by destroying the nearby cellular area these are like you know those monsters which want to eat they want to eat everything up. So, this radical oxygen or radical hydroxide they are desperate to get their valence shell filled highly reactive species they will get from nearby areas eat that area up they will burn that area up oxidation is basically burning you burn that area up and you in that process generate heat in that process burn in that process you destroy the surrounding area what is the surrounding area the surrounding area is the cancer cell the surrounding area is the cancer cell oxidation of cellular components takes place this highly reactive species which becomes reactive the hydrogen and the oxygen present they become reactive because of the presence of the free electron this is that free electron that this drug creates and this is a free electron that has that is stable that goes into a defect state intersystem crossing it cannot return back to its home because the spin is unpaired.

So, it needs to do something till it is losing its energy it reacts with the nearby hydrogen and oxygen creates free radicals free radicals are highly energetic compounds highly energetic chemical species and they in the process destroys the cellular components under which they are embedded under which they are injected resulting in cytotoxicity resulting in the destruction of those bad cells. So, the condition for this photosensitizer photosensitizer is the PDT drug which is sensitive to photo is the molecule that produces a chemical change in another molecule in a photochemical process meaning this change this change this triplet state that has formed is ready to create a change in another molecule the water and the oxygen both of them are changed into their reactive species into their free radical species which in turn is destroying the cells mind you the drug directly itself is not destroying the cell the drug is creating some sort of a triplet state something as such which is reacting with another molecule either water or oxygen which is then converted to which is then converted to reactive oxygen species to free radicals that is destroying the PDT drug is not directly destroying the PDT drug is there to create create a triplet state the triplet state will only happen when you have excited it with light. Therefore, therefore, by

itself without utilizing light this drug is harmless it is just there thereby you are trying to reduce the side effects or any kind of mistake just like that.

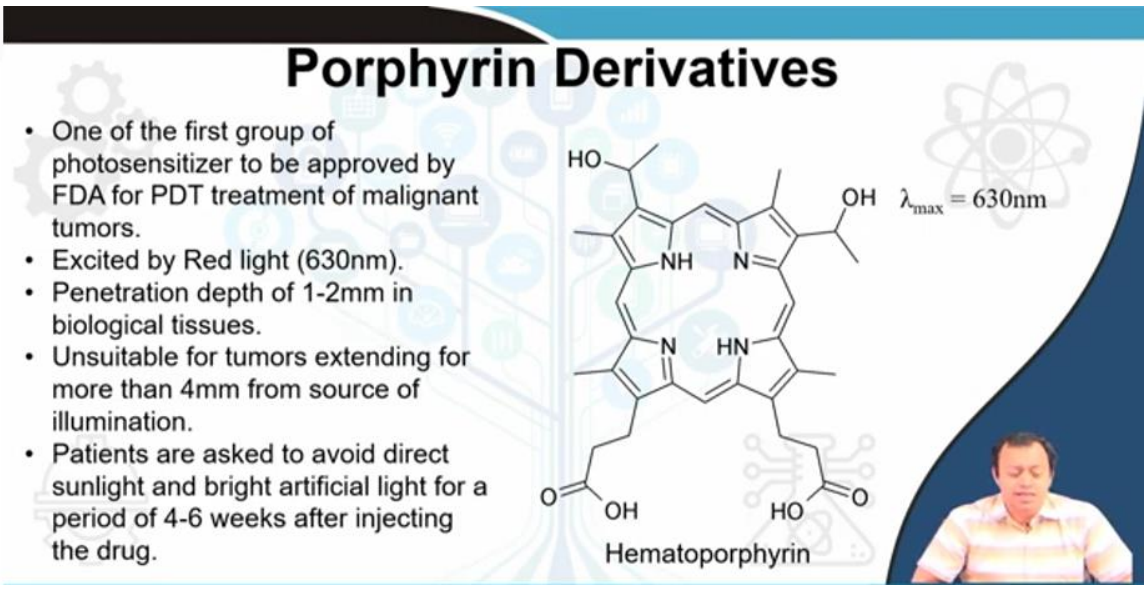


So, the photochemical process the chemical changes in another molecule in a photochemical process the photosensitizer the drug the PDT drug must have the ability to selectively accumulated into cancerous and precancerous tissue it must target specific cancerous cell it cannot randomly distribute anywhere it wants it should be ambiphilic to work both externally and internally the sensitizer should absorb significantly at 650 to 1350 nanometer. Now, this is important because here biological tissue do not absorb the light the light that you are sending to excite the drug should not be causing harm to the tissues by themselves they should not be the wavelength should not be absorbed by the tissue you know tissue absorbs light and they can then start oxidizing themselves and then that will be a side effect you do not need that.

So, 650 to 1350 a window wavelength window where the biological tissues are transparent they simply allow the light to pass through without any harm that is the window where the drug is absorbing. So, the tissue by itself is not getting harm the drug is absorbing inside the tissue the drug is creating a free triplet state the triplet state is attacking the hydrogen and water and the oxygen there in the surrounding area creating converting them into free radicals the free radicals is then eating away that area of the tissue that area of the cell resulting in resulting in burning of the tumor cell resulting in melting evaporation of the tumor cell. It should exhibit minimum toxicity in the dark minimum toxicity i.e. there is no light it should not have any toxic effect anywhere even in the cancerous area high quantum yield the number of photons it has absorbed should be giving enough amount of triplet states should not aggregate once PDT process is complete the drug should be rapidly excreted should from the body it should not just stay there it should not just stay

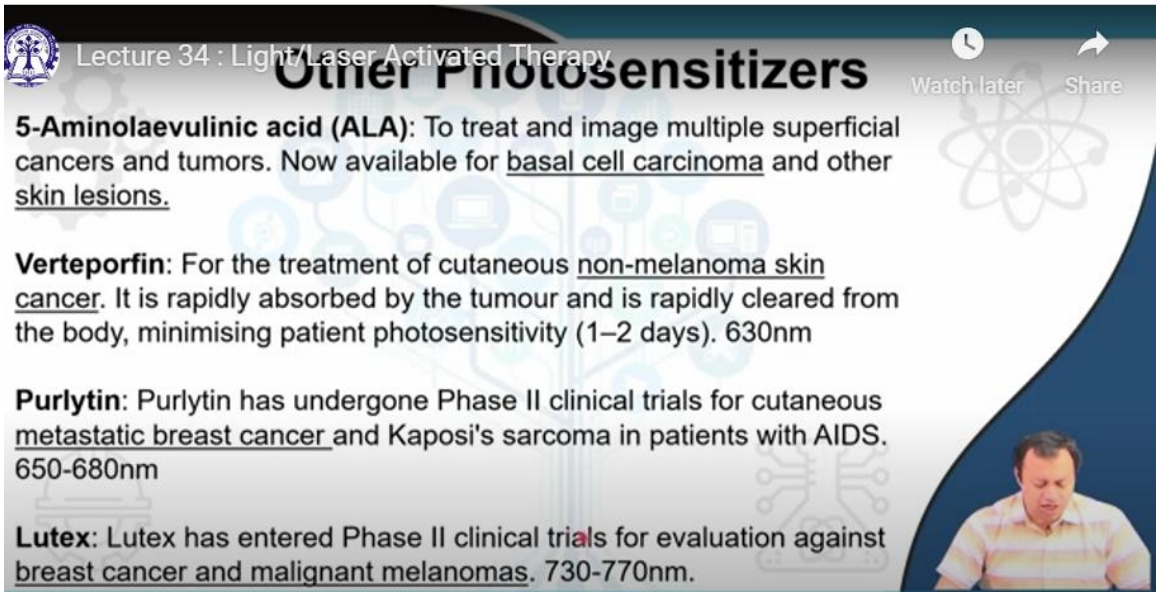
there after its work has been done.

So, these are the criteria's pharma companies pays substantial amount of money to you know create these kind of specific specific drugs that needs to be a specific attached to a particular area and b once the work is done once the triplet state is being done once the tissue is damaged once the tumor cells have been melted it should be renally discharged it should be removed.

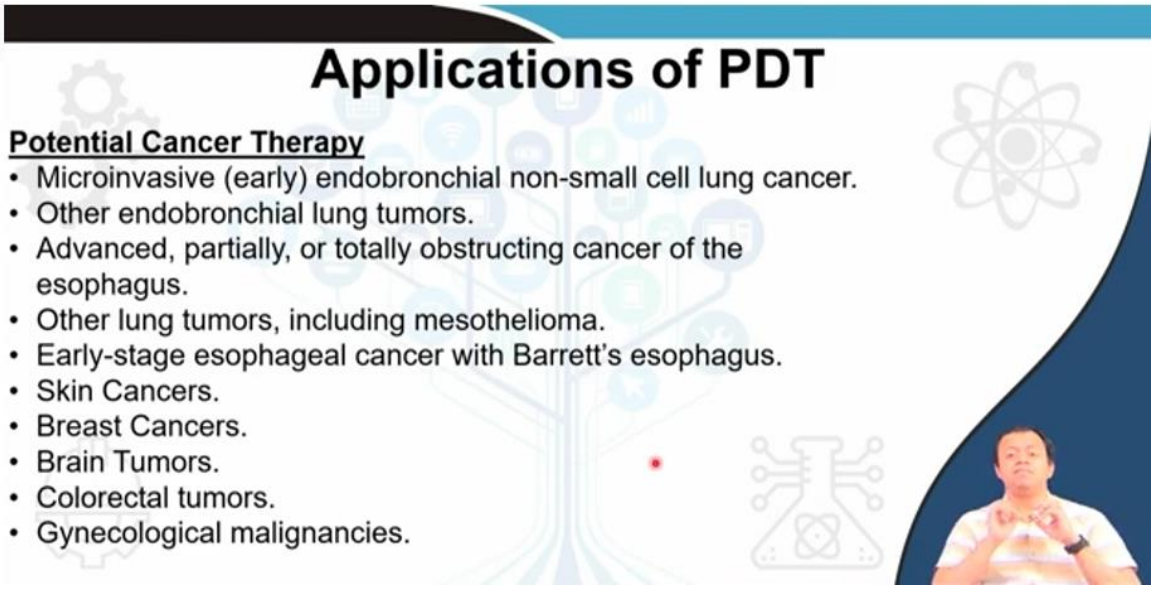


So, what are these types of drug example of these drugs one of the very first drugs are this porphyrine derivatives these are this porphyrine hematoporphyrin they are excited by red light the penetration depth. So, the porphyrine amount of porphyrine organic chemicals the amount of porphyrine is different in cancer cells this is a chemical basically the amount of this porphyrine is different in cancer cell versus in non-cancer cell. So, you can create some sort of a porphyrine based you know free some kind of a chain some kind of a molecule a free molecule that gets attached to that area where there is more porphyrine and its penetration depth is 1 to 2 millimeter in biological tissue. Now, this might be small to you, but actually 1 to 2 millimeter inside the biological tissue is quite high remember we are talking about micrometer or nanometer damage 1 to 2 millimeter is quite quite quite high upper layer of skin upper layer of skin is actually 1 to 2 nanometer.

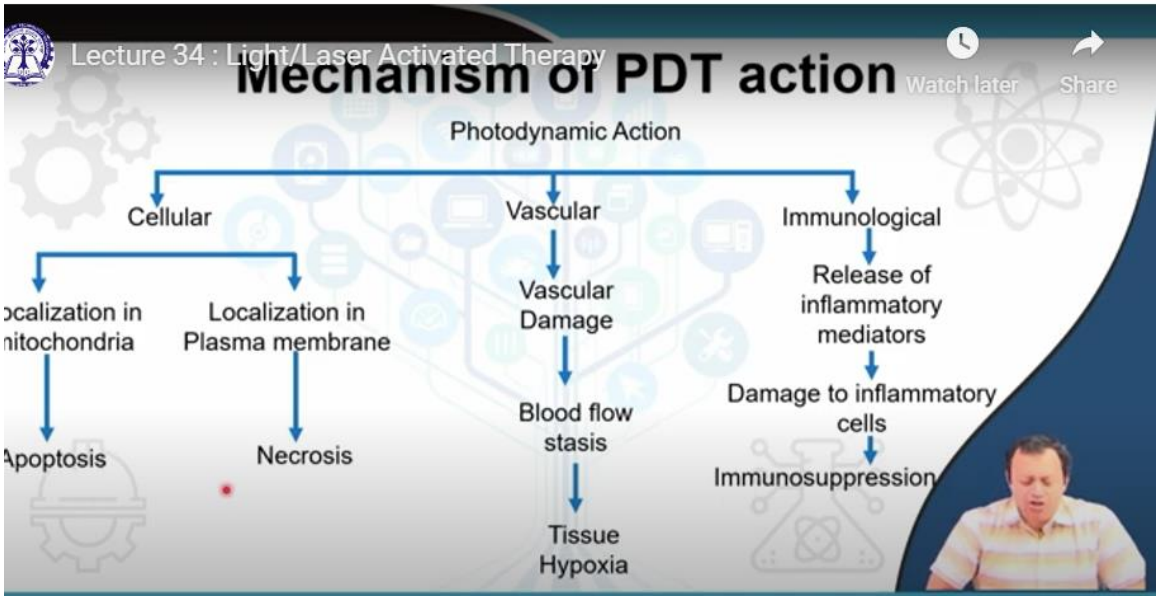
However, it is not suitable for tumor extending for more than 4 millimeter from the source of illuminations and patient are asked to avoid direct sunlight and bright artificial light for a period of 4 to 6 weeks after injecting the drug. So, you have to stay in an almost dark room for 4 to 6 weeks these are one of the first type of photosensitizer PDT drug.



Later several other types of drugs have come up pyrrolitin, lutex etcetera and they reduce the time from 1 to 2 days basal cell carcinoma skin lesion etcetera all could be treated 630 nanometers to 730 to 770 nanometers are the wavelengths that they absorb. So, they can be utilized for various applications.



So, as I said the potential for this application is quite high as long as you are able to make the drug selective at the same time you can send the light at that particular area. So, supposedly breast cancers, brain tumors, colorectal tumors, gynecological malignancies all of these has a potential to be utilized by treated by your photo dynamic therapy. The actual action is bit more complicated.

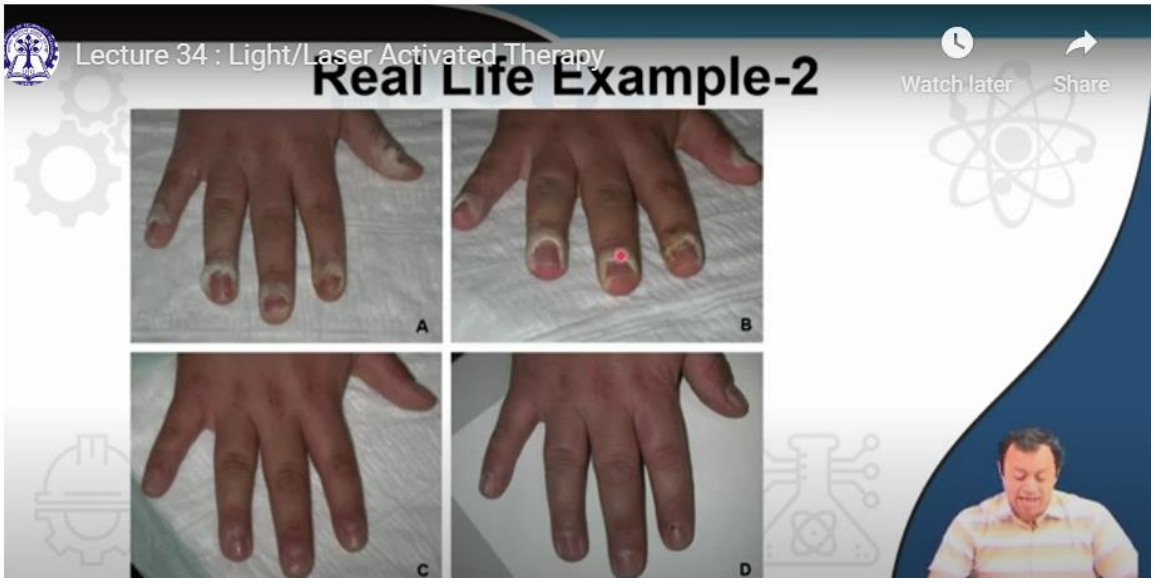


So, usually what happens inside the cell which is reacting with the reactive oxygen species the free radicals either the the the the reaction takes place in mitochondria remember mitochondria is the battery of the cell destroying the mitochondria resulting in apoptosis. So, apoptosis and necrosis how do I have from an electronics engineering background understood that necrosis is murder the cell is you know destroyed from outside some kind of additional external shock is given in which necrosis happens in which the cell raptures. Murder apoptosis is internal I suicide here the mitochondria which is part of the cell destroys and the cells dies whereas, necrosis in which the plasma membrane is simply broken down by the free radical and everything inside simply goes out and it gets killed.

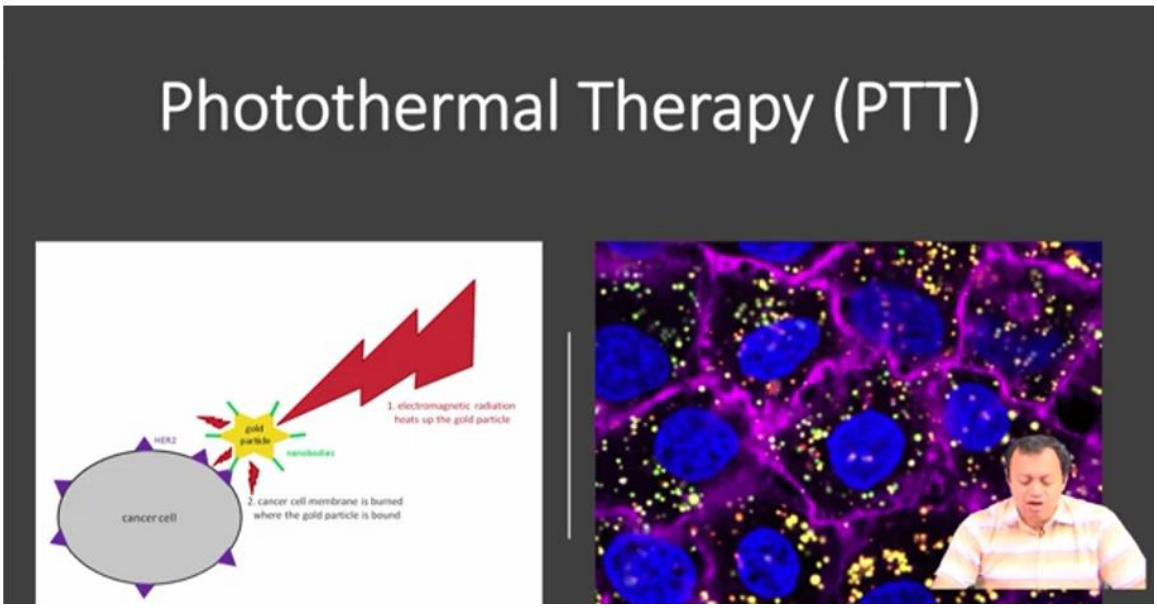
Here an internal organelle internal organelle mitochondria gets destroyed and thereby so, it is like heart attack suicide you can say heart attack here it is simply murder someone has you know slashed some part of the body and thereby the the cell has died. So, photodynamic action cellular wise is where either mitochondria is destroyed or the plasma membrane is destroyed in vascular like blood vessels etcetera you damage or you cut off abnormal blood vessels and thereby the blood flow is stopped to the cancer cells and the oxygen could also be restricted thereby on to the cancer cells and the cancer cells could not proliferate. So, you have a cancerous tumor which is connected with several blood vessels the blood is pumping oxygen etcetera into the cancer cell into the tumor region and the cancer is growing growing growing you destroy those blood vessels you destroy the blood vessels and starve the cancer cell of blood and oxygen blood carries oxygen. So, you cut off blood flow you cut off oxygen you cut off oxygen the proliferation the reproduction of the cancer cell could be reduced. Similarly, immunological autoimmune disease you know when bodies immune system attack itself that could happen inflammatory mediators can be can be can be generated.

So, here the photodynamic action has the capacity to damage the inflammatory cells these are the cells that called secretes some kind of antibodies that that that that that that attacks your own body cells. So, by destroying those inflammatory cells by destroying the inflammatory cells in several of these processes the immune system which has turned on itself bodies own immune system is attacking itself can be suppressed.

So, these are some real-life examples that I got from a Greek clinic which claims to do photothermal therapy. So, mostly I have skin so these acnes. So, previously medicine was applied to this place the patient was asked to stay in at home you also understand when it is skin and you can only use the ointment in the affected area not any other areas per say thereby you yourself are localizing it instead of injecting just apply the medicine the PDT medicine the photosensitizer to specific area these are Greeks I have taken it from the Greek clinic and these kind of things and then you excite light on to that the patient is asked to stay in a dark room more or less and then you apply light into it and you see after a week or so this treatment the same patient the the the the the process or the damage is controlled the therapeutic cure could have been found.

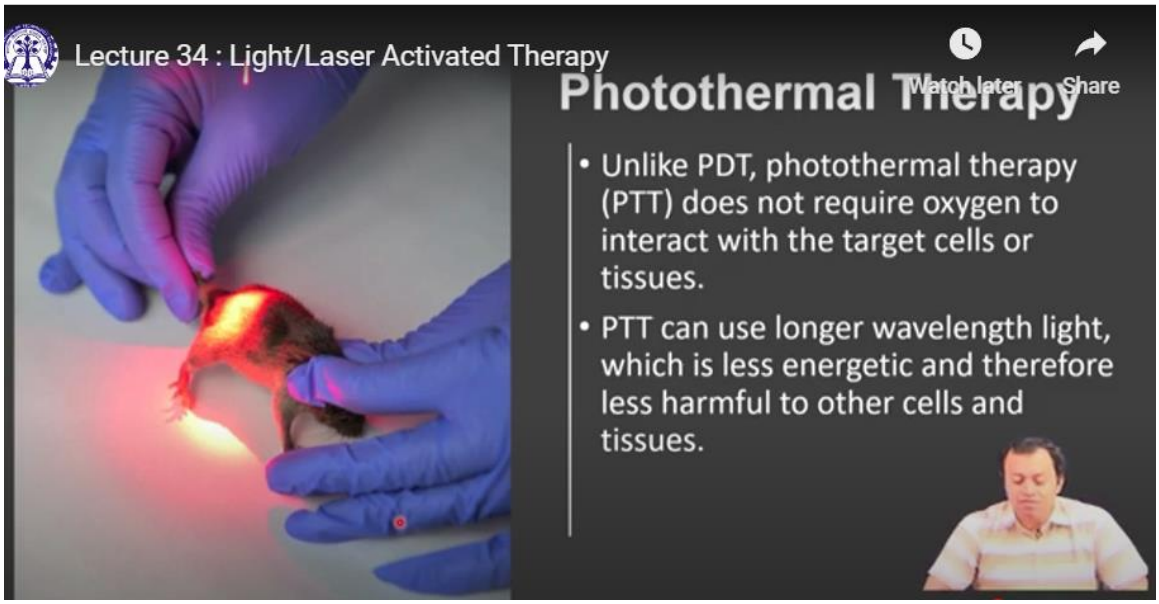


Another is this Warts I do not know medical student correct what is the in correct pronunciation this these are as I am being told some kind of fungal infection on to a fingers that can happen for many different causes working in farms unhygienic lifestyle not cleaning hands regularly you have fungal infections. So, medicine is applied to these areas and then light is being shown and you see you see it is more or less painless it is more or less painless because the chemical reaction that takes place does not cause much of a pain and at the end of the day it is very much localized. So, these kinds of real-life examples are available another thing that is coming up is photothermal

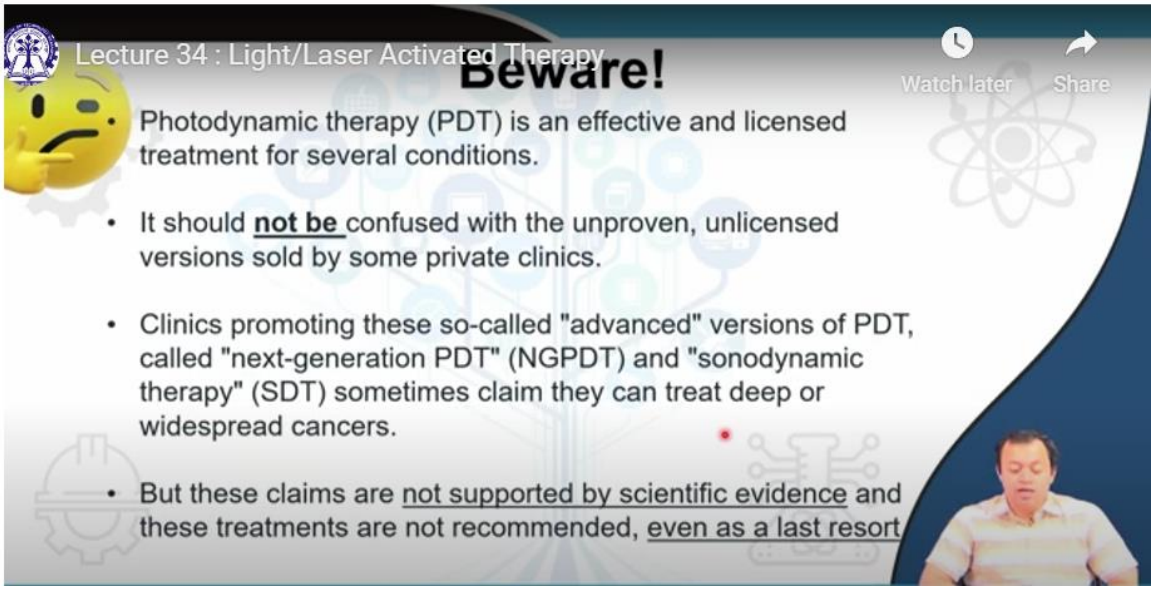


therapy previous one was photodynamic therapy is photo thermal therapy in which you put nanoparticle usually metallic nanoparticles inside the cancerous cells. This gold nanoparticles gets inside the cancer cells you send light these light heats up this gold

nanoparticles gold nanoparticles produces heat no oxygen is required gold nanoparticle these are cellular structure these are nucleus big nucleus usually indication of cancerous cell big nucleus. So, these gold nanoparticles are there you shine light the gold nanoparticle absorb the light and starts you know vibrating causing phonon or heat and that heat localized heat in so many different area damages the cell membrane resulting in death of the tumorous cell.



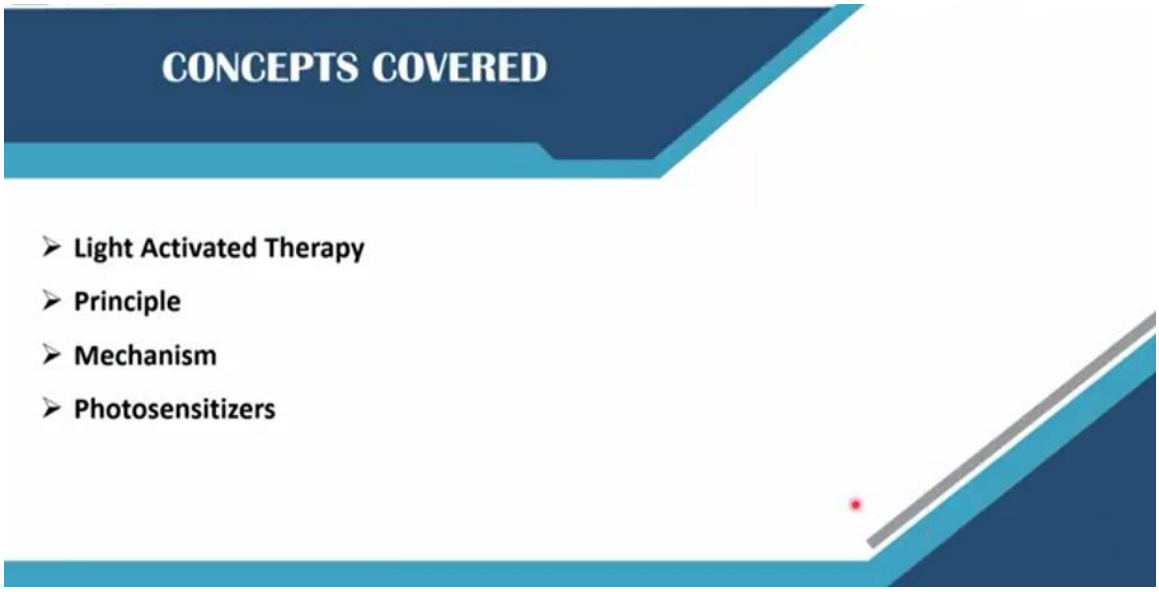
So, unlike photodynamic therapy photothermal therapy does not require oxygen to interact with the target cell it is purely thermal PTT can use longer wavelength of light which is less energetic and therefore, less harmful. So, this is an example where the gold nanoparticles or any metallic nanoparticles usually other things have also been tried, but gold or silver nanoparticles are more common they are being injected inside the live mouse and then from this from this fiber laser optical fiber based laser system light is shown laser light is shown on to this particular area and then you will obviously, dissect this mouse to see how much the tumorous area has been damaged. So, these are very very cutting-edge research and for those of you who are interested I ask you I strongly ask you to explore this further, but before you go I need to give a disclaimer that



remember photodynamic therapy as I showed is approved by FDA food and drug and administrative agency of United States, but this has been misused by so many quacks, so many frauds, so many pseudo doctors who claim to do light therapy and bring some kind of magical mumbo jumbo along with a light-based system aura and what not and thereby try to cure patients claim to cure patients. PDT is licensed PDT is medically valid the government medical agencies such as NHS national health system national health scheme of United States as well as national institute of health of United I think NHS is United Kingdom NIH national institute of health is of United States they utilize PDT. So, it is proven it is scientific it it it works in certain conditions that does not mean that you should go for it should not be confused with unproven unlicensed version sold in some private clinics this fraud is going on for a long time light based therapy certain bio photons are being sent and this bio photons are being imaged and then figure out that you have negative energy positive energy energy is energy equals to h nu any energy is equal to h nu there is no such thing as positive or negative it is like saying positive number or negative number if the vector is different I can understand, but there is no such thing as positive energy or negative energy or the aura is changed or the spirit level is changed and thereby certain things is going on if certain things like that exist I need to be convinced I have yet to see them properly scientifically reproducibly done yeah.

So, please please be aware of them there are so many advanced version of this next generation PDT where we chant something and then light is being put and different colorful lights like discotheque is been put inside patients and then you ask I am they ask you to pay you huge amount of money considering this as latest this is not this only go to proper medical personnel proper authorized hospitals to get photodynamic therapy or photo thermal therapy these claims these aura and bio photon are they are not supported by scientific evidence and these treatments are not recommended even as last resort. So,

please please be aware anybody who claim to be you know light based therapy because light based therapy has been misused abused and and and it has been sold to numerous people and they are simply being looted out of their fortune out of their money because people get desperate at at at at a certain position to cure their loved ones and anybody who claim to come up with a next generation of therapy and the easiest thing to tell a lie is to sandwich it between two couple of truths. So, photothermal therapy exist, but you utilize that photothermal therapies idea and create your own discotheque and then say that you know sit in front of this discotheque where colorful lights will fall in your body and you will get cured that is wrong. So, absolutely be aware of that and if you find any fraud case like that please please report to the authorities.



So, these are the topics that I discussed today and these are my references I will see you

in the next class. Thank you very much.