Mathematical Aspects of Biomedical Electronic System Design
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Lecture 17
Introduction to Biomedical Optics

Welcome everyone for the continuation of mathematical modeling for biomedical systems. Today, we are going to talk about the biomedical optics. We will try to learn what are the basics of biomedical optic field, we will talk about the current techniques about what people have currently been using as gold standard, that is the histopathological test.

And then, we will also talk about different optical parameters, that is, bulk optical parameters such as scattering coefficients, absorption coefficients and how we can use such kind of parameters to diagnose certain disease such as breast cancer. So, let us go ahead and see what view do we have.

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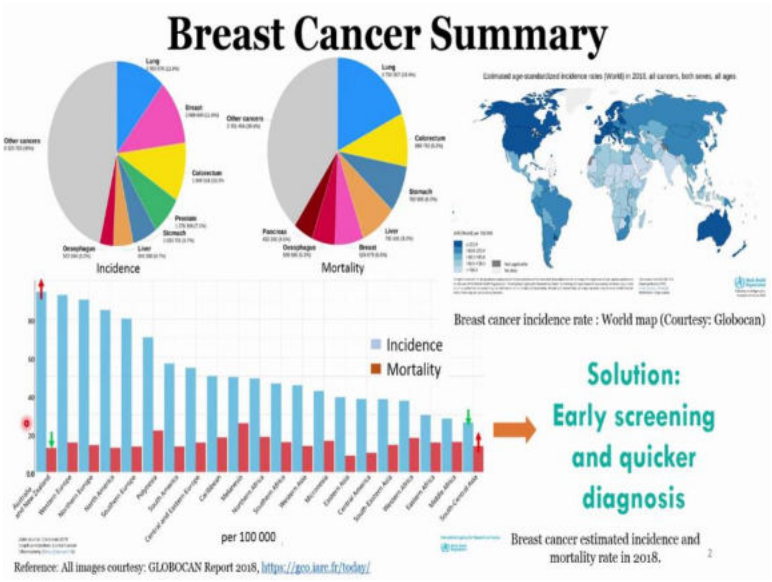

So, first thing is the why breast cancer? So, the, so let me just switch on the LASER pointer. So, as you can see breast cancer is the second most highest number of cases where you see the incidence rate. And in the case of mortality, is the number fifth, number of cases where you see the breast cancer over here.

Now, once you try to see what is the incidence and mortality rates throughout the rates. Now, what I try to do is, what I try to show over here is the profile of the different, different countries on the x-axis. And the y-axis, we have plotted the incidence rates in the blue graph. And the red graph is for the mortality.

What do we see over here? We see that for developing countries, such as Australia, New Zealand, Europe and America, you can see that there is large number of incidence rate as compared to the mortality. So, mortality is fairly less as compared to the number of incidence rates. But, if you see less developing countries or developing countries such as India, South Africa, what you see is that the incidence rates are lower but the mortality rates is higher than the developed countries over here.

So, why is this kind of a question that is arriving over here, that why the incidence rate, which is lesser, but then also the mortality rate is comparatively, or it is more as compared to developed countries. The answer to this question is about the early screening and quicker diagnosis for breast cancer disease. So, we are going to talk about how you can approach this breast cancer disease, how do you diagnose the breast cancer using the optical techniques.

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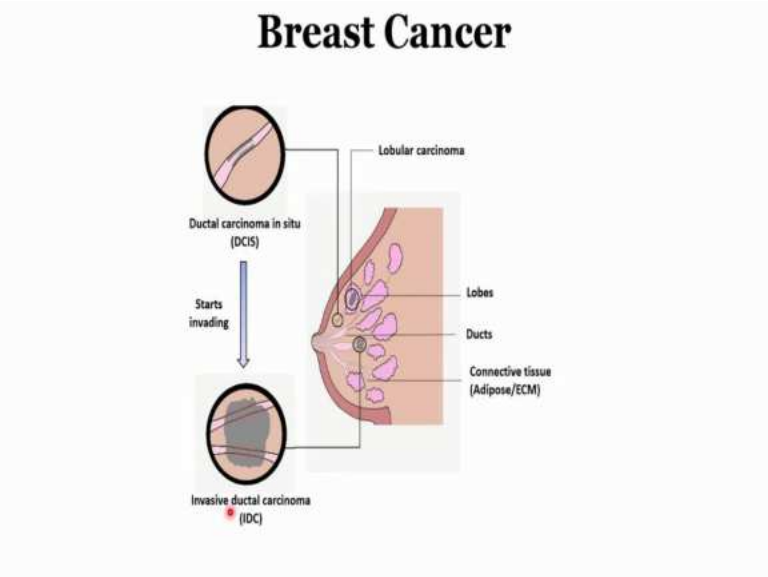

Before approaching the breast cancer with optical techniques, we should always know about the basics of the breast cancer and what are the different kinds of cancers that you can diagnose with the techniques that we have over here. So, this is how the anatomy of the breast looks like. What we have is the lobes over here. We, the lobes is where the milk is, is created and then it is supplied through the ducts to the nipple. And then, the other brown colored structures are the connecting tissues, that is the adipose and the extra cellular matrix.

Now, you can see the structures such as the grey structures that you see over here. It is seen in the lobes, within the ducts as well as when it is spreading out from the ducts. The first thing that you

see is the disease which is generated within the lobes and that is known as lobular carcinoma. And if I just zoom into the duct part over here and you can see over here the grey part over here, the grey region, which is surrounding to the inner surface of the ducts, and this is in situ. That is, it is still within the ducts. It has not started to spread yet.

And this is known as ductal carcinoma, in situ. It is also known as DCIS, in short. Once it starts to invade or come out of these ducts, then it is known as invasive ductal carcinoma. And around 80 percent of cases you see, such kind of invasive ductal carcinoma, when the breast cancer is diagnosed. So, let us go forward.

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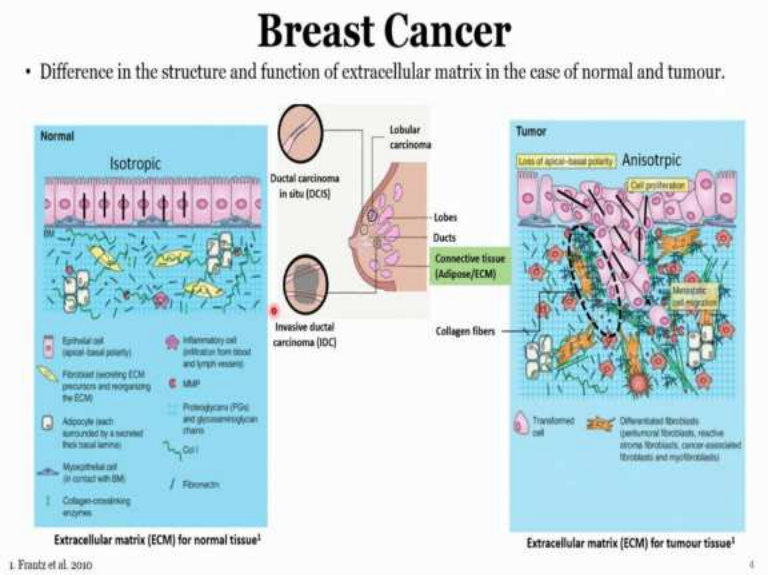

So, the first thing that comes in the mind of the clinician or the, then engineering person who is trying to develop a, a, a breast cancer diagnostic tool is that how do we differentiate these different, different types of cancer. Before do that, you should also understand, or one should also understand what is the constituents within each of these components of the breast cancer or the constituents of the breast, breast anatomy.

The first thing is the connective tissue, that is, the adipose as well as the extra cellular matrix. And this is how you, you, you see what is in a cartoon sketch that you see on the left side. In the case of normal tissue, what you observe is these epithelial cells or these basal cell membranes are like, very isotropic. That is, all, all are arranged in a very uniform manner over here.

As you can see over here, they are kind of polled to a certain direction over here. And that is a case when it is normal. You see all the other collagen fibers, you see the adipose tissues, the fibroblast, all of them are placed inside this basal membrane, that is, inside over here. And that is the grey part that you, not the grey but the brown color that you see over here.

But in the case of the cancerous tissue, what you see is, it is not isotropic anymore. What you see is anisotropic arrangement of the cancerous basal mammal, basal membrane cells over here. And then you can also see these collections of the collagen tissues which are surrounding these basal membrane tissues which are trying to go inside now the extra cellular matrix.

So, this is the main difference between the normal and cancerous tissue, or a tumorous tissue. A tumor tissue is basically which has still not spread through the other parts of the breast and through the body, through the lymph nodes. And it is basically very anisotropic. It is kind of arranged in a very random and unorganized manner.

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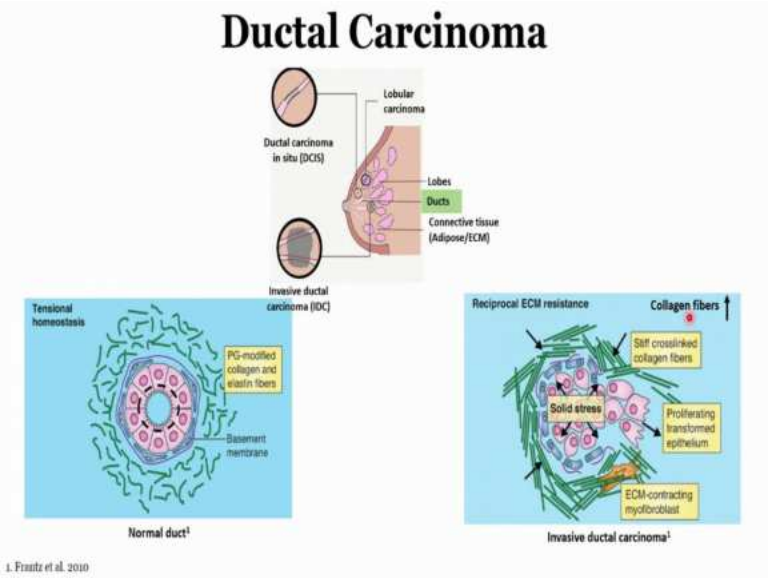

So, let us go next to understand the ducts. The ducts, when you try to see the anatomy of the ducts, you will get a stretched sketch, something like this. So, it is a kind of a circular cylindrical structure, where you, you see the basal cell membrane over here which is surrounding the, the ducts over here. And through the center, the milk which is generated by these, or created by these lobes, lobes is transported to the nipple.

So, this is a case when we are caught, we talk about a normal duct profile. It is nicely arranged in a circular manner. The stress being developed from the internal and the outer is like, equal to it maintains its circular shape. And the other part is, as you can see on the right side. What you see is a case when the duct is undergoing a transformation towards the tumor. So, what you see over here is again is a random nature or random arrangement of the ducts over here. No, no milk can actually pass through this duct over here because there is no more hollow space in the center.

You can also see that this basal cell membrane is now coming out of the, the collagen fibers that were nicely keeping surrounded by this, around this duct profile. But now it is kind of broken and the, the cells which are, which are now undergoing this cancer metastasis is, is now spreading to the other parts of the breast.

So, this is, what you see is the, the, now the stress is now equal, which is now coming out, towards outwards as well as inwards. So, it is now unequal, there is a change in the equilibrium balance over here. And what you observe is that the solid stress is trying to pull outwards and at the same time, the stress which is acting like a resistance by the extra cellular matrix is now point with, pointed inwards.

In addition to it, what else you can see is that there is large number of collagen fibers that are now being present in this structure over here. And this is going to be one of the main factor that we are going to take at a later stage, which changes the properties of this biological tissue, such as the density of the tissue, which eventually changes the optical properties of the tissue such as the scattering coefficient.

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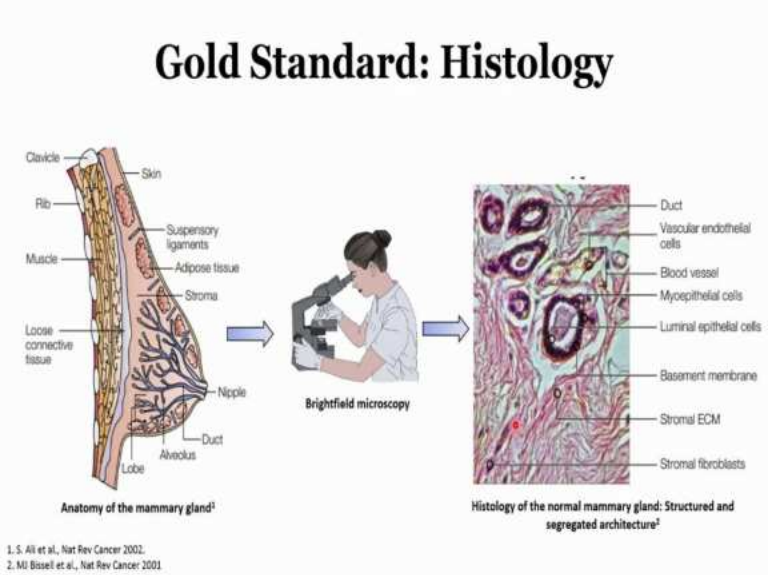

So, when we talk about how do we diagnose the breast cancer, there are different techniques. And the one technique which is used world wide is known as Gold Standard. The current gold standard to diagnose breast cancer, the type of the breast cancer, that is, the pathology of the breast cancer is to use the histology, the histopathology, where you have the H and E test. Hematology and Eosin stain.

So, what do we do is, so this, on the left you see the breast, in the case of a normal breast. And you, what you do is, you take a small part of this breast using the biopsy gun, or the biopsy punch, biopsy needle, needle. You cut it into a slice of 100s of micrometers thin slice of tissue, and then you stain that tissue, and then put it under the slid with the cover slip on top of it and see it using a Brightfield microscopy technique.

So, this technique is used to understand the pathology of the breast cancer. And this is, on the right side what you see is a normal breast cancer histopathalogical test. So, you can see nicely the ducts which are being formed over here. It is nicely circular over here. You can also see the blood vessels over here, that is a dark region over here, where the blood is flowing over here.

You can also see the myoepithelial cells, Luminal epithelial cells, that is outer and inner structures of the basal membranes. And this is the complete basal membrane over here. You can see the extra cellular matrix, and then finally you can see the fiber blast which is surrounding, or just lying around in the, in the stroma.

So, this is the case when we see the normal case of the histopathological results by, seen by the clinician. So, now, let us move ahead and see what are the different kinds of histopathological tests that you see once you are looking into an abnormal case or a diseased case. So, one by one we will go through and try to understand it.

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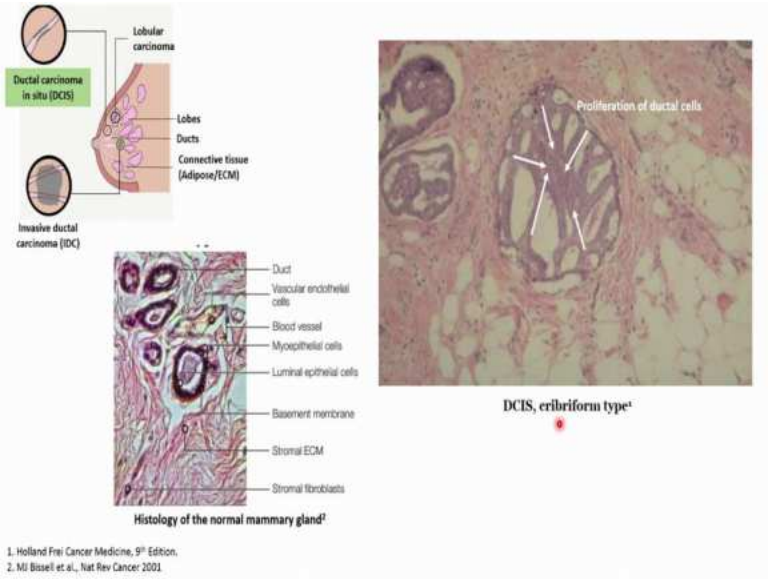

So, the first thing that you see is a ductal carcinoma in situ. So, what do we mean by ductal carcinoma in situ, is the cancer which is present, or the tumor which is present within the ducts, the grey part that you can see over here. Inner surface of these ducts over here which is not yet spreading to the outside the ducts. That is an important way to differentiate this with the other type of breast cancer. On the left side again, we have the normal case. But on the right now, we have something new. So, this is, what you see is again, so we just give few seconds for you guys to think about this, what is this?

Yeah. So, this is the ducts. But this is a duct in the case of a diseased breast. So, what you see over here is the surrounding over here is the, again the basal membrane, over here. But there is something else that you can see which is not seen in the actual case over here. That is, the normal case of the ducts. So, before proceeding further, you can just pause this video and just think about it, what is the difference that you see over here as, what, that you cannot see in this duct's profile over here.

So, what you see over here that is different is the proliferation of the ductal cells. So, you, earlier in the case of normal ductal cells you will the, a hollow in the center, as you can see over here. But

in this case, in the case of ductal carcinoma in situ, that is, the cancer, which is inside the ducts as of now, which is not spreading outside the ducts, is nor proliferating inside the duct cell and it is obstructing the flow of milk, if she is having a newborn with her.

So, this type of the ductal carcinoma in situ is known as cribriform type. And there are different, different pathologies of the breast cancer that we will discuss. And one of them is cribriform type, which you can nicely see within the histopathological slides, stain slides. Now, as you go on and create your own devices such as optical being one of these hypothesis to create such devices, it has the limitation to actually limit, to diagnose the type of the tissues. So, it becomes very, very challenging for the optical technology to actually also delineate or to, to specify which type of pathology of breast cancer is being present within the breast. And that is what you will see in, in the next few slides. So, there are a lot of different types of pathologies.

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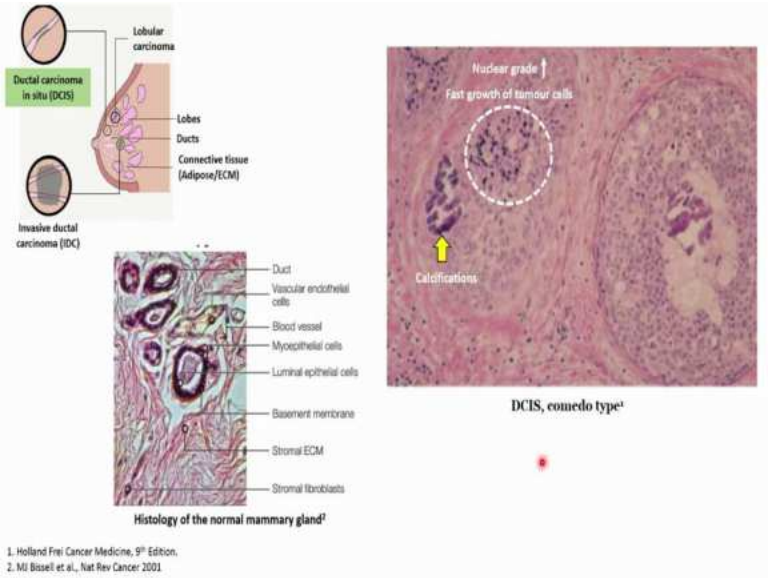

So, now, coming to the next type, is the, again, again it is DCIS, that is, ductal carcinoma in situ. And now here, you see something else. So, you can, you can pause the video for a few seconds and just try to see, what are, what is the difference that you see in, in, in this staining image, which you cannot see in this original or the normal case of the duct's profile over here.

So, what you see is a fast, again, this is the duct over here, ducts over here, ducts, and what you see over here, because of the staining, it is actually in dark blue color. The dark blue color is the tumor cells and its growth is now very, very fast. And that is why there is a large number of tumor cells within the ducts.

Again, it is surrounding inside the ducts over here and it has a very high nuclear grade, that is, the growth rate of the tumor cells is very, very high. In addition to it, what you see is the calcifications within, now being formed within the ducts. And that is also a very important part because calcification is also going to change the property, bulk property of the tissue, that is, the mechanical property of the tissue, eventually changing the optical properties of the tissue.

This type of the ductal carcinoma in situ, again within the ducts, it is not yet spreading outside the ducts. So, this is a DCIS, ductal carcinoma in situ. And this type of pathology is known as comedo type. There are a lot of other types of DCIS, which you can go and refer to the other books. But we can go to the other part, that is, now, the lobular carcinoma. That is present within the lobes, where the milk is generated.

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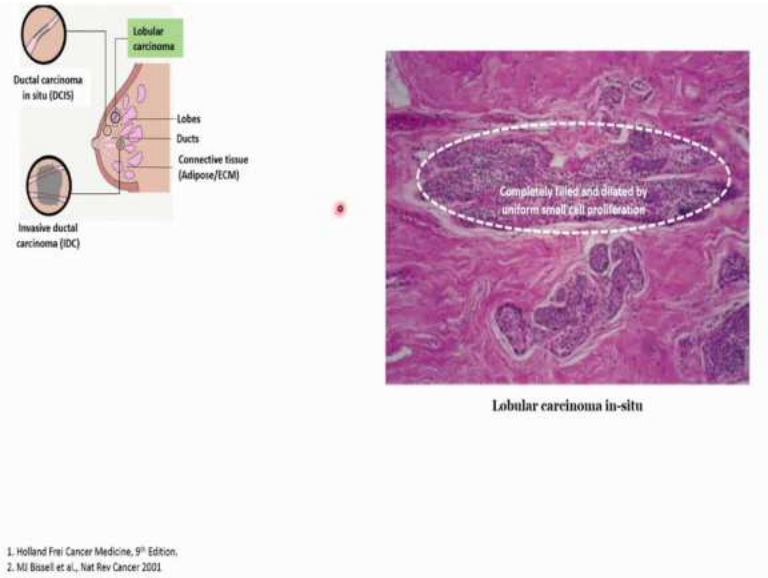

So, over here, again, you can just take some time and see what is the difference over here that you can see as compared to the lobes over here. So, you can see that it is now, the lobes is completely filled and dilated. So, it is also important to know that it is being dilated. And it is dilated because, or dilated means it is now increasing its own size, and that is because it is getting completely filled. So, there is no more space within these lobular cells or this lobular structure, and now it is trying to dilate or it is trying to increase its dimension.

And that is because of the tumor cells, which is being present within the cells over here. And now, it has proliferated throughout the lobes. But it is still not actually spreading out, and that is why is

it still in situ. So, we have lobular carcinoma in situ. So, it is still within the lobes and it is not spreading out of the lobes. So, let us go to the other part.

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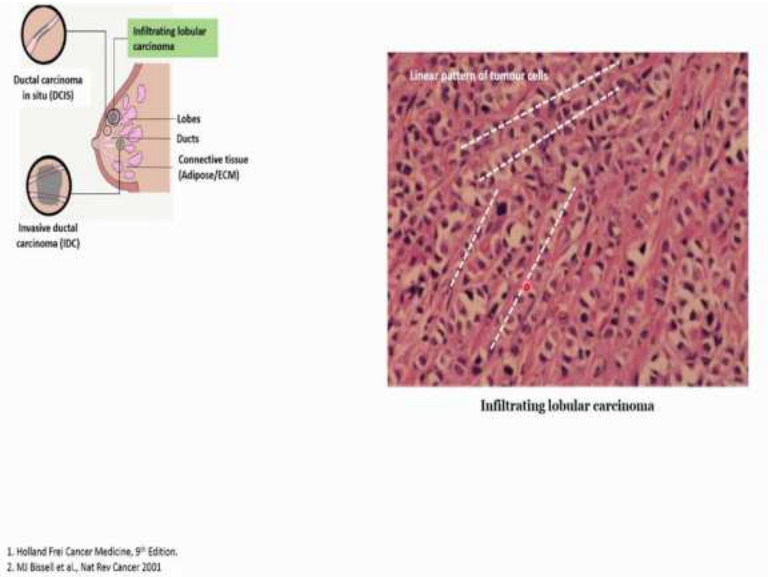

We talked about in situ lobular carcinoma. But once it starts to spread, what you see is something known as infiltrating. Infiltrating means it is now infiltrating to the other parts of the breast and then it will go to the lymph nodes and then it will start to go to the other parts of the human body. So, what, how do you differentiate this with the other cells, the histopathological tests that you saw?

So, again you can just pause the screen and just try to see how do you, what is the type of, of the arrangement of the tumor cells that you see over here. So, what you see over here is the linear pattern of the tumor cells. That you have not seen before. Earlier it was more or less random arrangement of the tumor cells, and very non-uniform arrangement. But in the case of infiltrating lobular carcinoma what you see is a linear arrangement of the cancer cells. So, this is a way to differentiate this pathology with the other pathologies.

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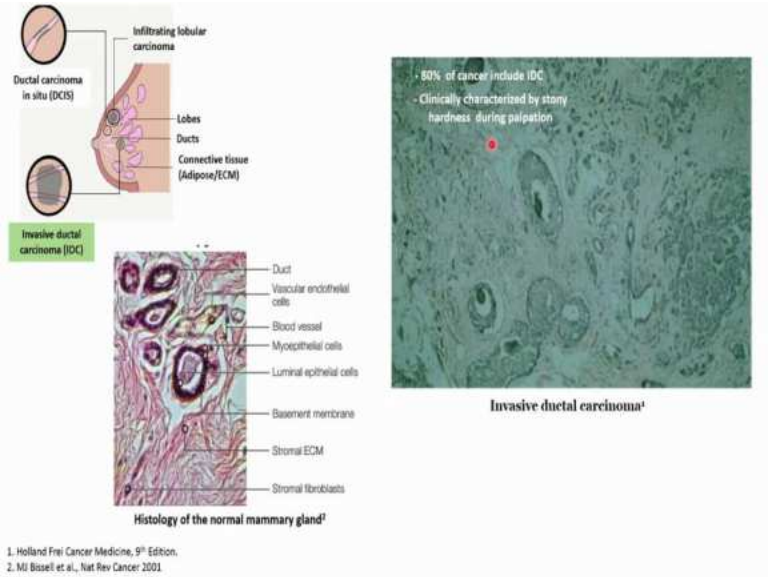

Now let us, let us go to the other, that is, the last one. And that is the invasive ductal carcinoma. And this is around 80 percent of the times that the clinicians are able to see this kind of, or they are able to diagnose the breast cancer with the invasive ductal carcinoma. And it is also famously known as IDC. That is Invasive Ductal Carcinoma.

So, again, how do you differentiate it with the other pathologies? So, this is quite simple. Over here, it is actually clinically characterized by stony hardness during palpation. So, palpation is a kind of procedure where the clinician tries to press the breast of the patient and try to see if there is some kind of a very hard structure, like a lump structure is present over here. And it is very difficult to actually differentiate through the pathology over here. So, let us go now forward to see the different types of techniques, different types of techniques other than histopathology where we are trying to use the, to diagnose the breast cancer.

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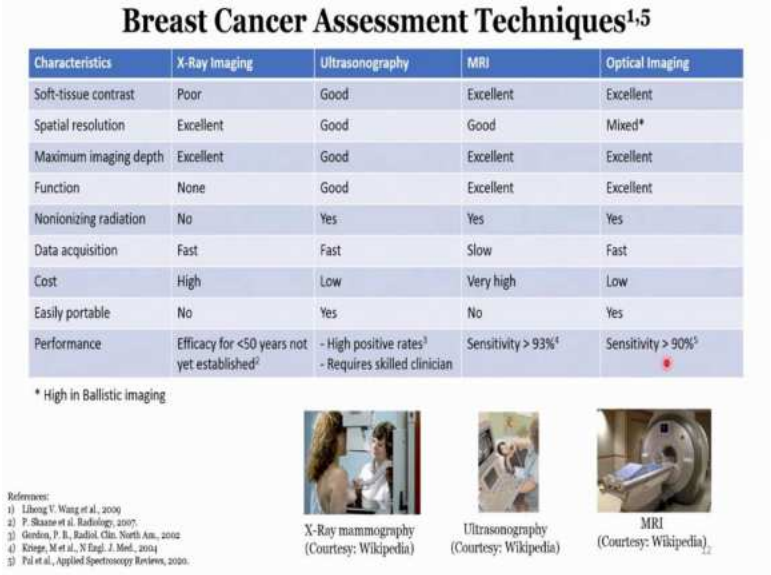

So, as you can see on the screen, there are different techniques. The first one is the X-ray imaging. Second is the ultrasonography, third is MRI, that is, Magnetic Resonance Imaging. And then finally is the optical imaging. In today's course, we will actually talk about the optical imaging. So, there are different characteristics that are defined for this assessment. For example, the soft tissue contrast.

So, in the case of soft tissue contrast, the ultrasound and MRI are like, very, very good as compared to the X-ray image. Even the optical imaging is very good in, in the case of where you want to characterize soft tissue contrast. So, for example, what does it mean is, you want to differentiate the tissue with the soft matters, or the soft cartilage that is present.

The next thing is the special resolution. So, how nice resolution that you can actually get after doing the imaging. So, in this case, the special resolution is excellent in the case of X-ray, and it is good in the case of ultrasound and MRI. But in the case of optical, it is mixed. So, what do we mean by mixed is that as you can understand, as you can, you will go, as you will see at a later stage, what we will observe is as the density of the breast is being increased, that is, the fat content is going to be more, in those cases what you will see is that there is more scattering. And as there is going to be more and more scattering, there is going to be loss of data.

So, that is one of the major challenge to actually diagnose the type of pathology that we were discussing sometime back. And low resolution is going to also affect our capability or our capacity to come to an informed decision. The next is the depth of image. In the case of X-ray, which is a

ionizing media, or ionizing approach, is excellent. It is able to pass through the tissue very nicely. In the case of ultrasound, it is good. And in the case of MRI again, it is kind of an X-ray, so it is of course, excellent.

In the case of optical, it depends on the operating wavelength. So, as you go on increasing the wavelength in order of mid-infrared regions, or near infrared regions, you go ahead with penetrating large distance through the breast tissues. At the lower wavelength, such as the visible wavelengths, in such wavelengths there is lot of scattering. So, it depends on which wavelength are you using for, over here, in the case of optical.

The functioning, so you want to also know the type of analysis that your, or your breast is performing. For example, you want to know the oxygen saturation. So, that is with respect to some work I am doing. For example, I am doing a muscular twitching of my hands and quenching my fist. In such cases what you will see is that my brain, for example, will work in a different way when I am doing a certain kind of function.

So, functioning, functional MRI is something new that has come and that is also something excellent, to understand how good, we are doing that particular function. In X-ray imaging that is not possible. In ultrasonography it is still possible. And it is excellent in the case of optical imaging. Let us see, now, which one is non-ionizing. Of course, X-ray is non, non-ionizing and ultrasonography is still, sorry, actually X-ray is actually ionizing and the rest of them is non-ionizing.

In the case of magnetic resonance imaging, we are using these electromagnetic fields with coil structures and with a particular frequencies over here. So, if you talk about the computer edit automation, that is the CAT scan, Computer Aided Technology. So, in, in such kind of CAT scan, it is still actually X-ray image.

Data acquisition is actually very fast in the case of X-ray imaging, ultrasonography and optical imaging. But in the case of MRI, it is comparatively, or relatively slow. Cost is very high for X-ray mammography. The dimension is also very high. So, the, it reduces the portability. In the case of ultrasonography, the cost is low, and it is still portable. In MRI it is, cost is very, very high. And it is not portable because the dimension as you can see on the right side is like, huge.

For the cost of the optical imaging is low because we use technologies such as LASERs as well as LEDs. And such techniques could be actually used to differentiate, or to quantify the bulk optical properties like scattering coefficient and absorption coefficient. So, the cost of the LEDs and LASERs are comparatively lower. And the dimensions of such sources are also very lower. So, it becomes portable.

So, you use LASERs and LEDs as a source, and detectors, you use infrared detectors, for example, or you can use the photon, silicon detectors, you can use photomultiplier tubes, all of them are kind of a detectors. Again, those detectors are small in dimension. And it is actually, because it is small, you can actually make it a very portable device.

Performance-wise, efficacy, means the concerns with the X-ray mammography is that the efficacy for, for people or women less than 50 years is not yet established because it is not advisable, X-ray imaging is not advisable for women which is less than 40 or 50 years old. In the case of ultrasonography, it has very high positive rates, requires skilled clinician to understand the results. The good part of MRI is that its sensitivity is very, very high. And again, the sensitivity of optical imaging, it actually is, is mixed. So, it depends on the type of technique that you use.

As we will see, there are different kinds of optical techniques, that is, continuous wave, we have time domain, as well as we have frequency domain types. So, in all the three types, when, the, when we use a certain type of technique, your sensitivity will change. So, in some of the cases people have reported more than 90 percent of sensitivity, which is like, very, very great.