Electronic System for Cancer Diagnosis
Dr. Hardik J. Pandya
Department of Electronic Systems Engineering
Indian Institute of Science, Bangalore

Lecture – 11
Fabrication of MEMs-based Biochip for cancer diagnosis

Hi ah. Welcome to this particular module. In a last module, what we have seen; we have seen the statistics about oral cancer and breast cancer, right and in this module let us see the screening techniques.

So, when I talk about oral cancer what are these screening techniques that are used to determine the cancer.

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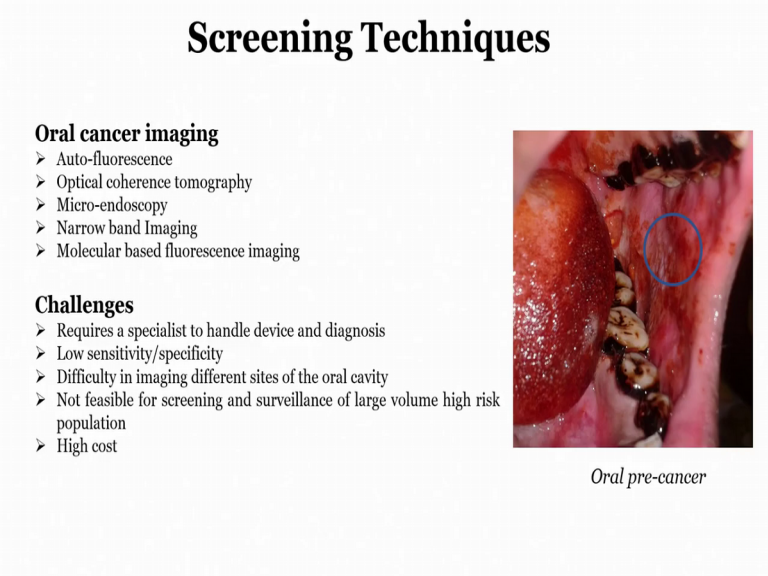

So, if you see the slide what you see here is the imaging techniques and there are different and kind of imaging techniques. First is auto-fluorescence, second is optical coherence tomography or OCT; next one is micro-endoscopy, narrowband imaging, molecular based fluorescence imaging, alright. So, these are the techniques that are used to screen based on imaging.

The challenges are that requires a specialized or specialist to handle device and the diagnosis, low sensitivity or specificity, difficult in imaging different sites, not feasible

for screening and surveillance of large volume high risk population and finally, it is a high cost.

Now, if you see here oral cancer or a pre cancer region which is right over this region, alright and it is kind of difficult to identify again.

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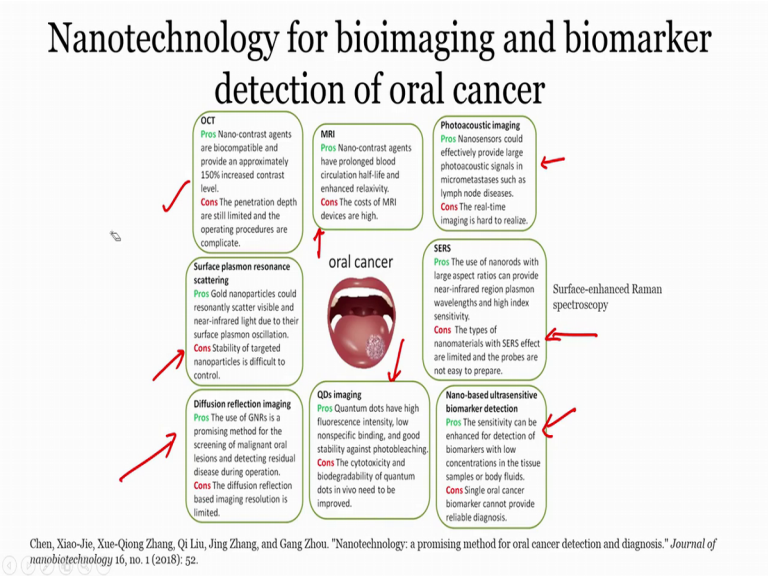

Chen, Xiao-Jie, Xue-Qiong Zhang, Qi Liu, Jing Zhang, and Gang Zhou. "Nanotechnology: a promising method for oral cancer detection and diagnosis." *Journal of nanobiotechnology* 16, no. 1 (2018): 52.

If I talk about nanotechnology for bio imaging a biomarker detection oral cancer which was published in journal of nanobiotechnology recently then you can see that there are several techniques that are compared here and the pros and cons of each of those were mentioned in the article ah. If we start from OCT then the nano-contrast agents are biocompatible and provide approximately 150 increased contrast level. That is the advantage. However, the disadvantage the limitation is the penetration depth are still limited and operating procedures are complicated.

If you talk about MRI, then the advantage is nano-contrast agents have prolonged blood circulation half-life and enhance relaxivity relaxivity while the cons are the cost of MRI devices are high, right. So, this is the MRI. If you talk about photoacoustic imaging in that case nanosensors could effectively provide large photoacoustic signals in micro metastases such as lymph node disease. However, the real time imaging is hard to realize.

When talk about surface plasmon resonance scattering, then gold nano particles could resonate scattered visible near infrared light due to their surface plasmon oscillations while the stability of target nanoparticle is difficult to control. When we talk about surface enhanced Raman spectroscopy the advantage here is that the use of nanorods with large aspect ratios can provide near infrared region plasma wavelengths and high index sensitivity. But, the limitation is in the types of nanomaterials with SERS effect are limited and pros are not easy to operate.

When you talk about nano based ultra sensitive biomarker detection the advantage is the sensitivity can enhance for detection of biomarkers with low concentration in tissue; while the disadvantage is single oral cancer biomarker cannot provide reliable diagnosis. We talk about diffusion reflection imaging the use of GNRs is a promising method for scanning of malignant oral encourage the essence, but the disadvantage is that the diffusion reflection based imaging resolution is limited. While when you talk about QDs imaging, we see that the quantum dots have high fluorescent density, low nonspecific binding, good stability against photo bleaching, but the disadvantages cytotoxicity and biodegrability of quantum dots in vivo need to be improved.

So, there are several techniques for oral cancer imaging, but can we come up with an alternative method where we can quickly do oral cancer imaging and which has more advantages and less of limitations and it is faster in terms of diagnosis, but anyway this is just an information.

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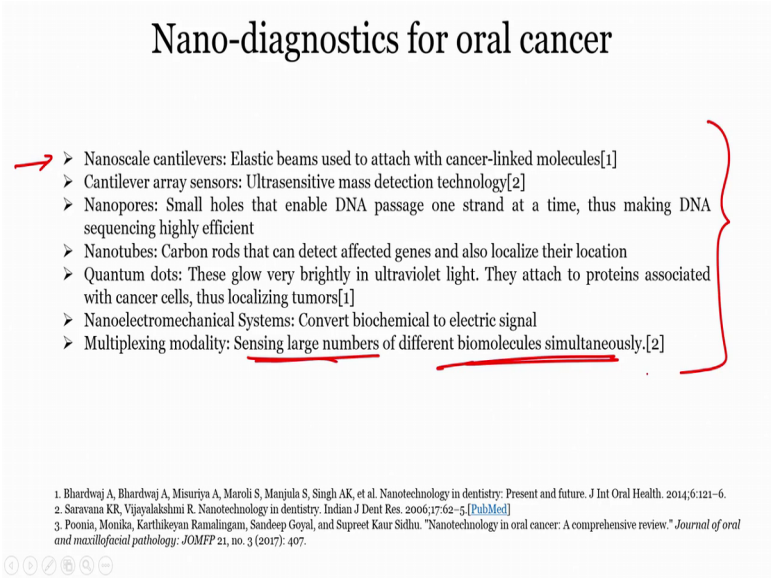

But, when we talk about non diagnostics for oral cancer sorry, nano-diagnostics for oral cancer then we have nano scale cantilevers which is elastic beam used to attach with cantilever linked molecules. We will actually see how we can fabricate micro piezoresistive microcantilever in this particular lecture series, we have cantilever array sensors with an ultra sensitive mask detection technology, we have nanopores which are small holes as enable DNA passage one strand at a time one strand at time and that is really interesting that is making DNA sequencing highly efficient.

We also have nanotubes. These are carbon rods that can detect affected genes and also localize the location. Where, quantum dots these glows very brightly in ultraviolet light. They attach to proteins associated with cancer cells thus localizing tumors. So, interesting right and finally, we have two more techniques one is called nanoelectromechanical systems like we have MEMs – micro electromechanical systems, we have NEMs – nanoelectromechanical systems, alright.

So, nanoelectromechanical systems where convert the biochemical to electrical signal we will see a micro MEMs based micro electromechanical systems based piezoresistive micro cantilever, alright piezoresistive micro cantilever. So, we will see in the slide somewhere how to fabricate those.

So, in the finally, multiplexing modality were sensing large numbers of different biomolecules simultaneously. We have several techniques, right. So, what can be alternative technique? What can be alternate technique that is our question.

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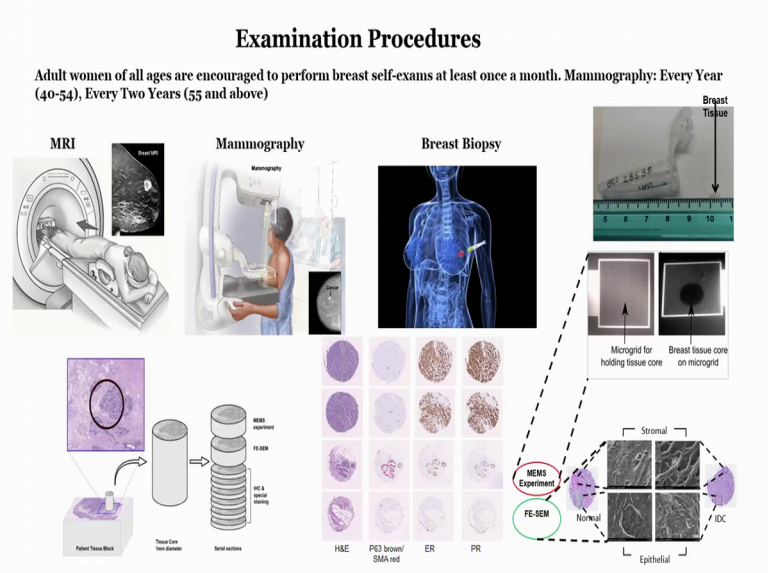

Now, when you talk about examination procedures for breast cancers, but women suffering from breast cancer then now you see one is all or adult women of all ages are encouraged to perform self breast self exams breast self exams I am sorry, at least once a month at least once a month. I told you right, for the abnormality in the breast. Then mammography this is every year for 40 to 54 and every 2 years 55 and above, right. So, this is what is advised to go for mammography ah.

There are different techniques I like I told you one is MRI where you can see the suspected region, there is a mammography and then there is a breast biopsy. If there is suspected region I can see here right, then the patient is asked for the biopsy, but the tissue is taken out with the help of a biopsy needle and once the tissue is out then they go for different biomarkers like I said H and E, P63, SMA red, estrogen, progesterone, alright and when there is a H E biomarkers as well and when all three biomarkers are absent is called Triple Negative breast cancer, ok.

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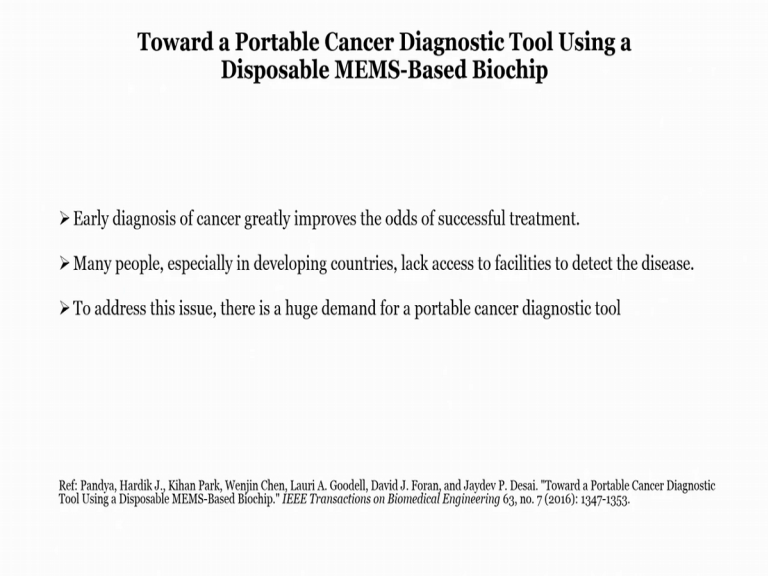

So, once we discuss about this, let us see what are the tools that we can fabricate that we can fabricate to understand the change in the tissue properties and to understand those chips or sensors you need to thoroughly listen to the earlier lectures where I taught lithography in detail, masculine in detail which is used for fabricating masculine in a UV exposure, right and you would understand the bulk micromachining and surface micromachining lectures, right.

So, this these those are my previous lectures which I finished and you would just go through those lectures once again to make sure that you understand when I say let us do soft lithography, let us do hard lithography, let us do soft baking, hard baking, exposure for photoresist coating, positive photoresist, negative photoresist, bright field mask, dark field mask RIE, DRI right, different thermal evaporation you should immediately get idea that what we are talking about. Still I will show you the process flow so, it becomes easier for you when we are looking at the chip design.

Now, if you see the early diagnosis of cancer greatly improves the odds of successful treatment. Many people is for especially in developing countries like access to facilities to detect disease and there is huge demand of portable cancer diagnosis tool.

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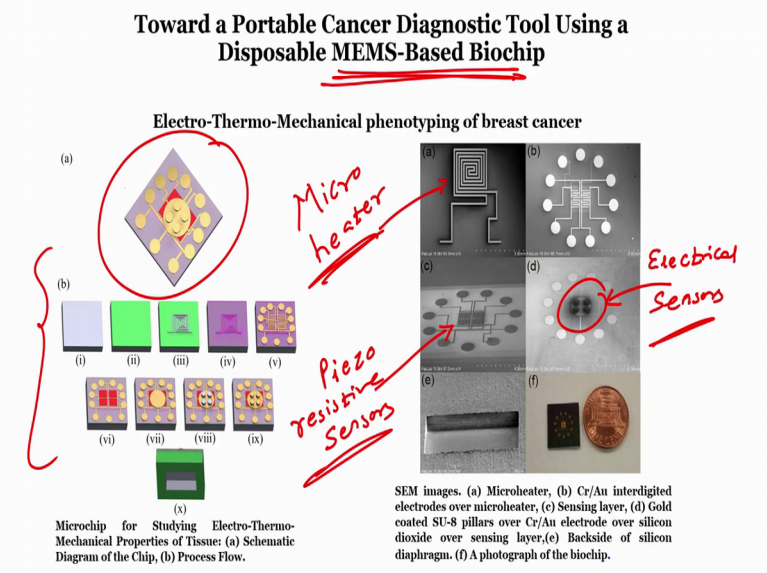

So, when you say that how about oh we develop a chip. We developed a chip, right that can make that has a micro heater that has or that is indicated with this is a micro heater, micro heater. This is a biochip, MEMS-based bio chip indicated with a micro heater indicated with piezoresistive sensors, piezo resistive sensors and electrical sensors, right. Let us understand this process, this process where we can develop or fabricate a MEMS-based biochip indicated with these three sensors; one is we call micro heater, second is piezoresistive sensors and third one is electrical sensors and then we will see why we are developing such a system or such a such a bio chip and how it can measure the change in the tissue properties.

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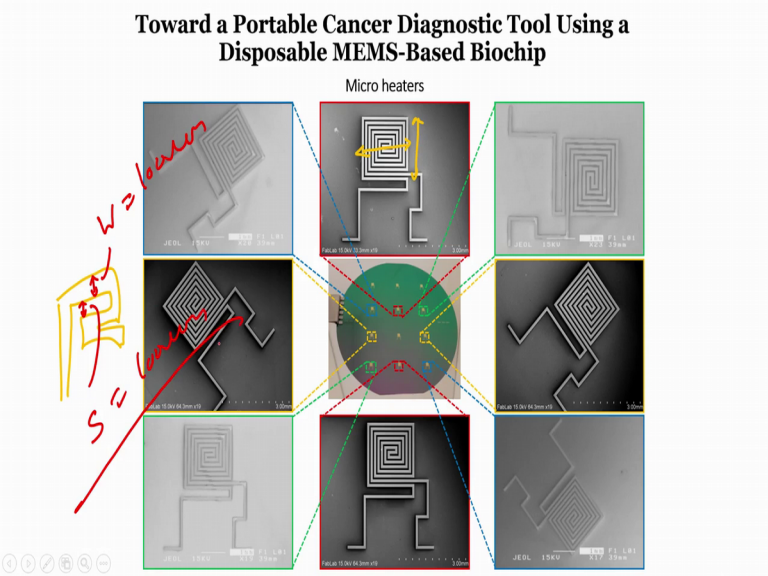

So, I will just open a new slide, alright and I will start teaching you how to fabricate a micro heater followed by piezoresistive sensors and followed by electrical sensors, guys. So, let us see here alright.

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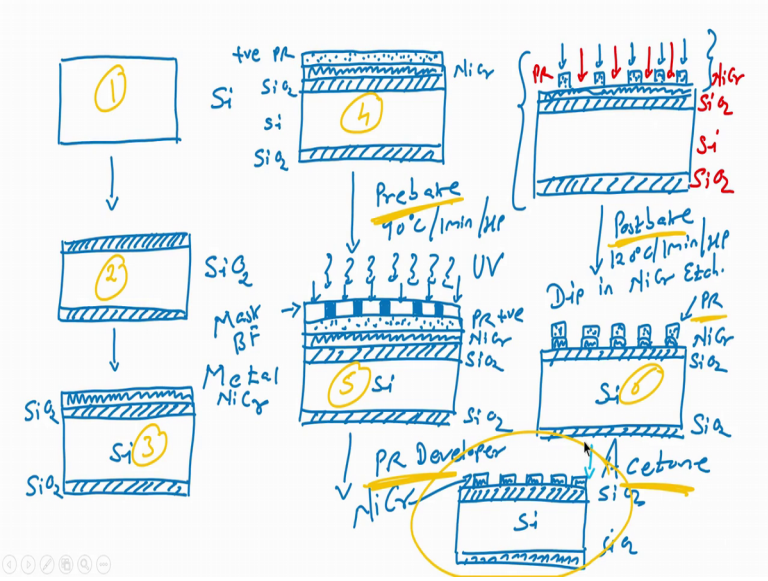

So, this everything this bio chip is made up made or fabricated on is fabricated on a silicon; silicon is a substrate. So, the first step is I take a silicon substrate, next step is to grow silicon dioxide correct because we cannot deposit a metal directly on silicon you know that. So, first is silicon, next is grow silicon dioxide. This we can grow silicon

dioxide using thermal oxidation right thermal oxidation. Next step we are to what is it process what I am teaching you I am teaching you how to fabricate a micro heater all right.

So, on this becomes a oxidized silicon chip, right. We will deposit a metal. This is metal. Now, since it is a heater we prefer nichrome Ni C r, right. This is silicon, this is SiO 2, this is SiO 2 right. Next step next step is to spin coat photoresist, right. I had to I have explained you this thing in ethnography is it becomes lead I hope it becomes little bit easier for you to understand the process flow that I am drawing here. This is positive photo resist, this is my metal, right this is my positive photoresist. So, I will just use dots to represent it, alright.

After positive photoresist what is the next step? Next step is pre bake pre baking at 90 degree centigrade for 1 minute on hot plate, right when you do that after that next step is UV exposure, right. But, we do UV exposure what we have to do we have to load a mask load a mask such that we will protect certain area and we will etch the unwanted areas, correct. So, we load a mask such that we are protecting the area and we want to etch the remaining area that is unexposed.

Now, since it is a positive photoresist is a positive photoresist what did I taught you last time, that when you use positive photoresist the unexposed region becomes stronger. So, this one is your mask, if I exposed with UV UV light, right what will happen, the unexposed region will become stronger. So, if that is the case after that what is my next step? My next step will be unloading the mask and what kind of mask this is? This is a bright field mask. Bright field mask after exposure I had to go for photoresist developer I will dip the wafer in photoresist developer. What will happen? The unexposed region would be stronger and the exposed region would be weaker.

So, silicon dioxide, correct and then we have micro and then we have photoresist. As you can see the unexposed region is still there right after developing in photoresist developer and the exposed region which is this region 1, 2, 3, 4, 5 and 6 exposed region got developed, you got etched um. After this next step is post bake. Post bake is done at 120 degree centigrade, 1 minute on hot plate. Next step is after next step is to dip the wafer or dip the wafer dip in nichrome etchant nichrome etch or let us etch the nichrome. What will happen? If I dip this wafer in nichrome etchant and the photoresist that is here which

protects the nichrome below it will keep protecting nichrome below it and the nichrome which is directly exposed will get etched.

So, what will I have? I will have a wafer. I will have a wafer silicon dioxide is there, silicon dioxide, right nichrome, but this is not correct because when you are etching it the nichrome etchant what you will have you will have this structure, right 1, 2, 3, 4, 5 let us draw it again, right and this is your nichrome and over that what you will have? Over that you will have a photoresist, right. So, this is your photoresist.

As you see the nichrome which was not protected by photoresist which was not protected by photoresist got etched um. So, this region what etched right in the nichrome in this region got etch this is nichrome Ni Cr then we have photoresist then we have SiO 2 we have silicon we have SiO 2, correct. So, after this what is the next step? Next step is that I will I will dip this wafer I will dip this wafer in acetone. When I dip this wafer in acetone then the photoresist will get stripped off. Photoresist getting stripped off will give me a wafer let me draw it again SiO 2 silicon; SiO 2 and this is my nichrome. What I am getting I have fabricated a micro heater I have fabricated a micro heater.

So, if we quickly go once again through this slide. What we see? We took a silicon wafer, right, then we have grown silicon dioxide. We have deposited metal using thermally operation, then we have spin coat photoresist on it followed by a pre bake, right. Pre bake is right over here and followed by a loading of bright field mask exposing with UV, photoresist developing, followed by a after what is developing, then what we have done? We are done post bake, right. After post bake we have etched the nichrome in a nichrome etchant and once we do that then a nichrome will get etched from the region which is not protected by photoresist and after that we are etching or stripping of the photoresist by dipping the wafer in acetone to get our micro heater to get our micro heater.

So, how this micro heater looks like let us see that and then we will continue in the next module. These are the micro heaters which are fabricated on an oxidized silicon wafer and as you can see the each micro heater is the this one and talking about this one by this one is 1.5 by 1.5 millimeter and the width and the spacing is 100 micron by 100 micron. So, width when I talk is a coil width, like this right coil is going and then it goes here and let us say it goes here like this is the spacing. When I say if this is a coil, this is the width and this is the spacing, alright this is the width, this is spacing width is 100 microns,

spacing is 100 microns; 100 microns by 100 microns see this is what is a what we have advocated micro heater and I have already told you how the fabrication of micro heater what is the process flow for that.

So, in the next lecture or module I will teach you how to fabricate a piezoresistive sensors over micro heater because our idea is to have a micro heater or idea is to have a piezoresistor and sensors or micro heater and on that we have to have electrical sensors, right. So, this is these are stakes. These are stakes, ok.

So, just go through this particular lecture once again and I will catch you in the next module where we will discuss more about how to fabricate the piezoresistive sensors. The ultimate idea is to once a biochip is ready how can you place the tissue and understand the change in the tissue property. So, this is all about understanding the change in tissue property, but we should require a sensor and that is what we are learning in this particular modules, alright. Till then you take care. I will see you in the next class. Bye.