Meet the Professor

Professor Pierce Chow: neo-adjuvant and adjuvant therapy for hepatocellular carcinoma—current evidence

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Professor Pierce Chow (Figure 1) is Senior Consultant Surgeon at the National Cancer Center Singapore and Singapore General Hospital and Course Director at the Duke-NUS Graduate Medical School, Singapore. He is also Senior Clinician Scientist with the National Medical Research Council, Singapore.

Professor Chow has published extensively on hepato-biliary cancers and gastrointestinal stromal tumors and carried out both preclinical and clinical research on brachytherapy in hepatocellular carcinoma (HCC) and pancreatic cancers. Currently, Professor Chow is the protocol chair of a 26-center investigator-initiated phase III trial that compares a selective internal radiation device (SIRsphere®) against molecular targeted therapy (sorafenib) in locally advanced HCC. In 2012 he was conferred the National Outstanding Clinician-Scientist Award in Singapore for his research on hepatocellular carcinoma.

Figure 1 Professor Pierce Chow

HBSN: Can you give us a brief general description of the current status of neo-adjuvant and adjuvant therapy for HCC as well as your own experiences?

Prof. Chow: Adjuvant therapy in HCC is extremely important. The outcomes of liver resections for HCC have really improved a lot, especially in the last 10 years, a phenomenon we established through meta-analysis and published last year. Currently the five-year overall survival rate with resection for HCC within the Milan criteria is around 67%. But one of the main problems with HCC is tumor recurrence which occurs in more than 70% of patients and is the cause of death for most of them. Recurrence comes from two sources. Firstly, it can come from the original tumor that has metastasized. Secondly, new tumors can come about even if you have successfully eradicated the original tumor because the liver is cirrhotic and there is in oncology terms, field change in the liver. Because of this, adjuvant therapy after potentially curative resection is extremely important in order to decrease the chance or speed of tumor recurrence. But HCC is a very heterogeneous disease at the molecular level although we seem to treat HCC as if it were a homogeneous disease. You know, at the molecular level, there are many subgroups within HCC.

Adjuvant therapy for most solid cancers is very well established. For example, you would not think of not giving breast cancer patients adjuvant therapy after surgery. You also always do it same with colorectal carcinoma. But unfortunately the data for HCC is very sparse. We conducted a meta-analysis under the auspices of the Cochrane Collaboration (an international collaborative group) on neo-adjuvant and adjuvant therapy in HCC and published the results of our meta-analysis in 2002 and updated this in 2009. Unfortunately there are not very strong data to support the routine use of adjuvant therapy of any type in HCC. There were one or two trials which were

promising. But they needed to be collaborated by bigger data sets which have not been forthcoming.

Currently, there are very few clinical trials in adjuvant therapy as compared to clinical trials in inoperable HCC. In fact the field is still wide open and clearly, this is an area that we have to look into. Of course you can approach adjuvant therapy in different ways. You can use physical therapies, for example using radiation therapy. You can also approach it using trans-arterial chemotherapy and there are clinical trials on that. But the really useful way is to personalize the adjuvant therapy. HCC tissues are available after resection and can be used to identify subgroups of patients through biomarkers which offer targets for therapy. I think this will be the way it is going to be done in the future. To deliver adjuvant therapy assuming that HCC is a homogenous entity is really not scientifically sound. In breast cancer you never will do that. Similarly for HCC, we have to pursue research into molecular subtypes in HCC and look for biomarkers. Thus, in future adjuvant therapy can be targeted in this manner. Currently the data is very sparse and I will be reviewing the data in this afternoon in my lecture.

HBSN: Some surgeons believe that neo-adjuvant therapy can maybe be helpful for other cancers like breast cancer and colon cancer but may not be very beneficial for liver cancers. How much evidence has been collected in the research and clinical studies to address these problems?

Prof. Chow: The answer is both yes and no. I think the concept of neo-adjuvant therapy is very important, especially in liver cancer. In liver cancer it is very clear that if even you do the surgical resection well, the outcomes of early stage liver cancer and intermediate stage liver cancer are very different. For breast cancer or colorectal cancer, as well as any other solid tumors you will consider giving intermediate stage patients neo-adjuvant therapy to downstage the tumor before resection. The long-term outcomes with the downstaged tumors are better. However when considering data from clinical trials we need to be careful. Early phase trials are very difficult to extrapolate. When confronted with the rigors of randomized controlled trials, many promising therapies fall by the way side. So if you look at randomized controlled trials, there is actually no positive trial for neo-adjuvant therapy in HCC. But I think this is also where we can see most promise. We have a very large liver cancer trials group (the Asia-Pacific Hepatocellular Carcinoma Trials Group) currently running our 6th multicenter trial. For our next trial, we plan to do a neo-adjuvant therapy study. Based on our experience with down-staging of tumors using Y-90, we have proposed a clinical trial in this manner. While it is right to say that there is no neo-adjuvant therapy in HCC, I would also say that there is a great need, a compelling need to look for efficacious neo-adjuvant therapy.

HBSN: So you have done a lot of research on novel brachytherapy therapy. Would you like to briefly introduce this subject and give us a general overview of this?

Prof. Chow: Liver cancer is actually very sensitive to radiation, in fact much more sensitive to radiation than to chemotherapy. But delivering radiation to a deep-seated organ is full of challenges. For example, the usual way we deliver radiation is through external beam radiation, which means that you lay the patient on a table and you shine radiation on the body. In order to reach that deep-seated target of yours with an adequate radiation dose, you may end up radiating and injuring a lot of surrounding normal tissues. This collateral damage limits the delivery of adequate dosage to the tumor. The alternative way of delivering the radiation to the tumor is to introduce the source of radiation right into the tumor. If you remember your physics, radiation obeys the inverse square law. With every cm away from the radiation source, the radiation energy drops significantly. If you are able to deliver the source of the radiation directly into the tumor, what you are able to achieve now is to give an adequate radiation dose to the tumor and yet cause minimal harm to the non-tumor part of the liver and to the non-cancerous surrounding organs. This is known as brachytherapy. In practice there are two ways to deliver radiation therapy in this manner and we have conducted research with both these approaches. One way is to inject the radiation source directly into the tumor and this may be carried out via a percutaneous route. We have positive phase II clinical trial data using this approach. The other way is to introduce the radiation through an artery supplying blood to the liver and the tumor. Of course, this approach is particularly useful in liver cancer because liver cancers are supplied almost entirely by the hepatic artery. In this approach, you will introduce a catheter through the femoral artery in the groin and advance the tip to position within the tumor. You can then deliver your radiation source right into the tumor avoiding radiating normal liver and other non-cancerous organs. I think these approaches are very promising. Radiation

therapy, like surgery is ablative or physical therapy—it doesn't matter as much what molecular subtype the tumor is. Surgery removes the tumor physically although recurrence depends on the biology of the tumor. Radiation therapy is ablative therapy, more similar to surgery in that sense. I see a lot of promise in radiation therapy and the challenge is on translational research to be able to deliver that radiation to exactly where you want it to be. If there is a good biomarker for the cancer and you can raise an antibody to the biomarker, you can then label the antibody with the radiation source. You will then be able to target it even more successfully. So I see a lot of promise in radiation and brachytherapy for liver cancer. This is complementary to systemic therapy. While current radiation therapy can target a mass lesion, you cannot target individual cells. Until you use antibodies, you can't target metastases well. I think we will see all these developing in our professional lifetime.

HBSN: Thank you very much!

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