ROLE OF LIQUID BIOPSY IN CANCER MANAGEMENT

A panel of 4 qualified doctors led by **Dr. Tan Yew Oo** from Farrer Park Hospital, Singapore, presented their case reviews on the role of liquid biopsy in cancer treatment. NGS was described as a technology used to access the sequence of DNA in genes and is used mainly in metastatic cancer to determine the mutation in a tissue sample of the tumor. The aim is to select treatment according to the genomic alteration of the tumor.

Dr. Toh Chee Keong talked about liquid biopsy in lung cancer. He defined ***liquid biopsy*** as any tumor-derived material that circulates through the blood or any other body fluids. Circulating tumor cells-CTCs and cell-free tumor DNA-ctDNA are most commonly studied after being extracted from the blood. Amplification, deletion, and translocation, etc. can be done. He further discussed the need for liquid biopsy for sufficient tissue for molecular biopsy.

With this new technology comes the benefit of targeted therapy. This means that we can identify the mutated gene involved in each individual, be it EGFR, ALT, KRAS, or any other, and then select inhibitors to target these mutants. Liquid biopsy also comes in handy for clinical use, especially when there's insufficient biopsy tissue or a high risk of biopsy complication. It can also prove beneficial in checking therapy progression, monitoring targeted response therapy, and resistance.

ADVANTAGES	DISADVANTAGES
• Non-invasive	• False positives
• Limited biopsy tissue required	• False negatives

In August 2020, FDA approved the 1st liquid biopsy NGS testing, Guardant360CDx and Foundation One liquid biopsy.

Dr. Hsieh Wen Son, further enlightened on the role of liquid biopsy on gastrointestinal tumors. He continued discussed biomarker testing, with emphasis in colorectal cancer. To determine the on the utility of liquid

biopsy, the ability to detect molecular alterations in blood and tissue biopsies in a large group of approximately 1200 patients was compared. The results showed a a high correlation between the genetic abnormalities found in the tissue biopsies and blood samples suggesting that liquid biopsy is reliable in certain situations. He discussed the results of the *Triumph* study, and *Heracles* study, in which liquid biopsies correctly identified patients with colorectal cancers which haboredHER2 amplification. These heavily pretreated patients were in turn able to benefit from combinations of anti-HER-2 directed therapies such Trastuzumab and lapatinib in terms of tumor shrinkage and control.

In addition to identifying potential targets in tumors which can be exploited for treatment, liquid biopsies to can also be used to help predict prognosis and to monitor for recurrence in patients with cancer. One such test is a liquid biopsy using the Signatera platform. , In this platform, common mutations in a patient's tumor are identified and quantified in the blood. Patient with detectable tumor specific mutations after resection of localized colorectal cancer have a relapse rate of 80% while those patients with undetectable mutations after surgery have a much lower relapse rate of 30%. This platform can also detect tumor recurrence up to 16.5 months earlier than CT imaging. These results may allow us an opportunity to intervene to prevent relapse by giving adjuvant treatments in high-risk patients. He then concluded by summarizing how the ability of liquid biopsy to identify, optimize, and monitor treatment response can play a role in GI cancer treatment.

Dr.Tanujaa Rajasekaran reviewed prostate cancer management via liquid biopsy. Various studies are done, and according to them, treatments must be chosen depending on the biomarkers involved. A biomarker (prognostic and predictive) is a characteristic that can be measured to indicate a biologic response and also a response to therapy. In particular to prostate cancer, prognostic biomarkers which are of importance are performance status, LDH, visceral disease, presence of pain, etc. The aim of these biomarkers is to give us precision oncology, that means choosing the specific treatment for a particular patient, for instance choosing between

chemotherapy or secondary hormonal agent. The example that was quoted in this regard was the response of PARP inhibitors to BRCA1/2 alterations.

She talked about the three pathways this heterogeneous disease can take.

- DNA repair pathway
- P13K pathway and
- Androgen receptor pathway (the most important)

From CTCs, we can measure Androgen receptor splicing variants, AR-V7 being the most common one. A small clinical study was done looking at AR-V7 using an ADNA test in which half of the patients were treated with Abiraterone and other half with Enzalutamide, and presence of AR-V7 was measured at baseline and PSA50 response was compared. This study was further done on a larger group of patients, and it was concluded that it serves more as a prognostic biomarker rather than a predictive one.

Another study also established that patients with a higher proportion of cell-free DNA have a worse prognosis than patients in whom cell-free DNA cannot be detected in the blood.

Some other cohort studies were discussed and it was concluded that biomarkers must be incorporated in the clinical practice because their clinical validation is limited.

A Q&A session was conducted at the end.

Dr. Toh Chee Keong explained the difference between MET exon 14 skipping mutation and MET amplification in lung cancer. MET inhibitor works very well for MET exon 14 skipping mutation and is approved by FDA. For MET amplification, MET polysomy works better.

Views regarding companies trying to promote the use of liquid biopsies for early detection of cancer were shared. Although they appear attractive, they may be associated with unintended consequences such as unnecessary anxiety. The opinion was there may be a lot of players leveraging on this wave of excitement, trying to look for cancers when there isn’t any and that one must be cautious.

Thoughts on using ct-DNA testing in somebody who is on adjuvant therapy were asked, and whether it can be used as a standard clinical practice. To this, one of the panelists agreed on having done this for high-risk patients but only for educational purposes or to rule out the high-risk patients but it was established that it cannot be advocated as the standard of care yet.

Regarding the prospect of replacement of tissue biopsy with liquid biopsy in the future, as the standard for cancer diagnosis, the consensus was that in certain situations, it is possible to make a treatment plan with a molecular profile for instance in the case of germline vs somatic mutations, but ideally one must do tissue biopsy because the former has its limitations.

The panelists sounded hopeful with respect to future advancements in this field.