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Report on Our Publication in Science Reports

The progress in oncology has been possible to a very large extent due to translational research – a multi-disciplinary and many times multi-institutional collaboration. Most of the translational research is done in the developed world, and we see very little of such work coming out of India although we have a large pool of clinical material, clinicians, and research facilities. This seems to be because of little or no orientation and exposure coupled with lack of laboratory attachment/facility to our clinicians, unlike in the West where a clinician spends substantial time in laboratory work in most academic centers.

My interest in translational research has been making me explore avenues to collaborate with various institutions and other departments in our own institute. Such work requires a good team of compatible minds. Our excellent clinical hospitals and many basic science institutions in India have been working in their own isolated spaces, with hardly any interaction to answer clinically relevant questions.

I was lucky after many years to find researchers in Dr. Prashant Kumar from the Institute of Bioinformatics and Dr. Annapoorrni Rangarajan from Indian Institute of Science in Bangalore, who were interested in working on the common idea.

Several people in the West have studied circulating tumor cells (CTCs) and their significance in patient outcomes. There has been no reported work on CTCs from India so far.

Researchers have shown correlation of CTC numbers and progression-free survival and overall survival across several tumor types, but substantial work does not exist due to the complexity involved in studying CTCs.

Dr. Prashant has worked earlier on CTCs and Ajay from his laboratory was one of the workhorses for this project. Dr. Annapoorni with Tamasa and myself along with Dr. Deepak and Dr. Abhishek from my department were the other main workers.

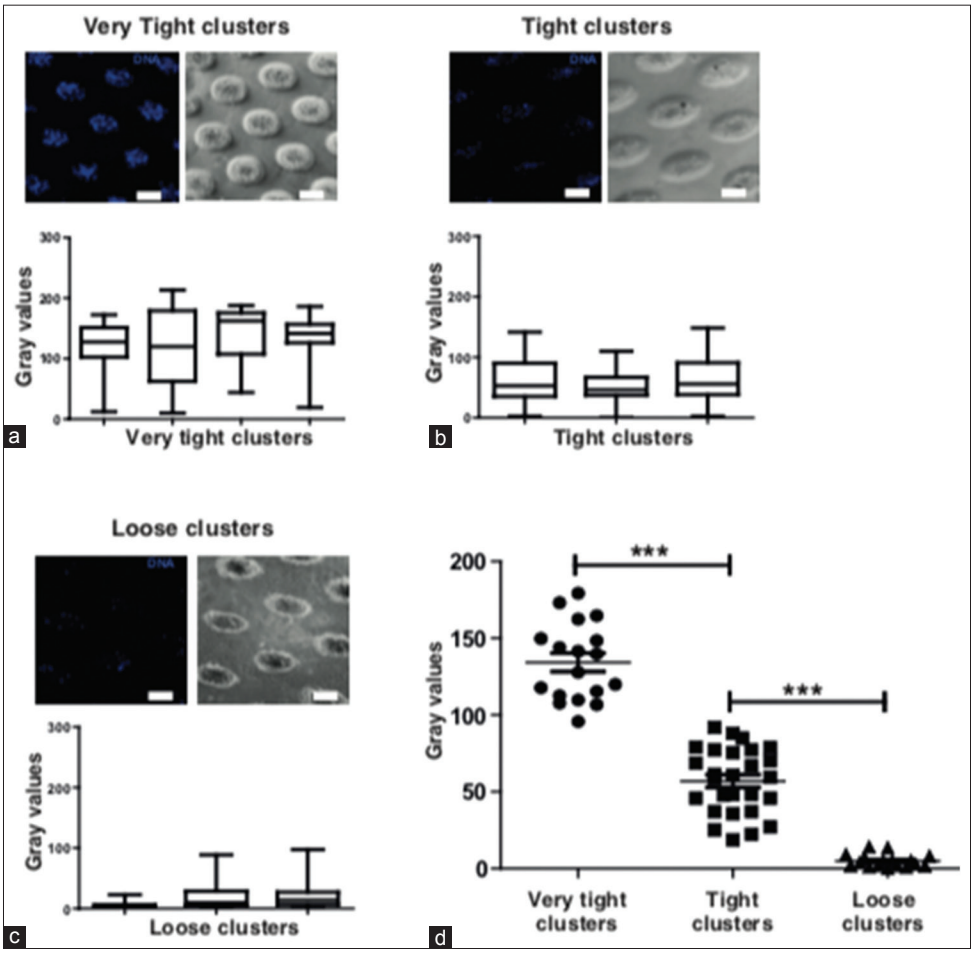

Figure 1: Cell cluster characteristics. (a) CTC's in very tight clusters, (b) CTC's in tight clusters, (c) CTC's in loose clusters, (d) Median gray sclae values based on DAPI staining intensity of the three cluster formation of the CTC's as shown in a, b and c respectively

This work is a proof of concept in the following contexts, firstly that multi-institutional collaboration involving clinicians and basic science researchers is possible in India. Secondly that CTC research, although perilous can be effectively undertaken in our country that could ultimately help our clinicians and patients.

The work essentially consisted of obtaining blood samples from metastatic breast and lung cancer patients on the day of starting systemic treatment, after three cycles, after six cycles, and longer in some patients.

The patients were followed up for the assessment and treatment as per our institute guidelines. The CTCs

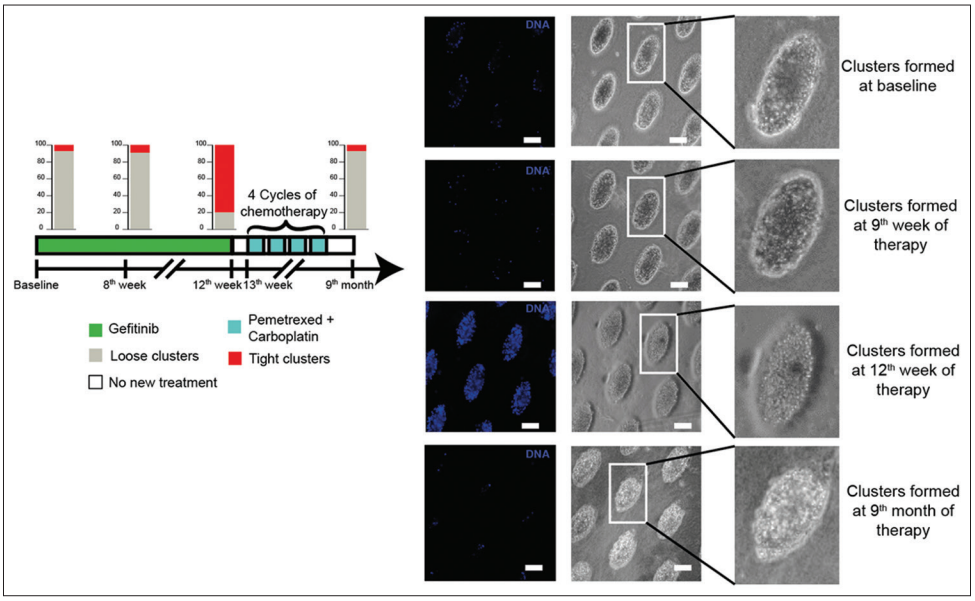

Figure 2: Response to gefitinib in nonsmall cell lung cancer and correlation to cluster formation

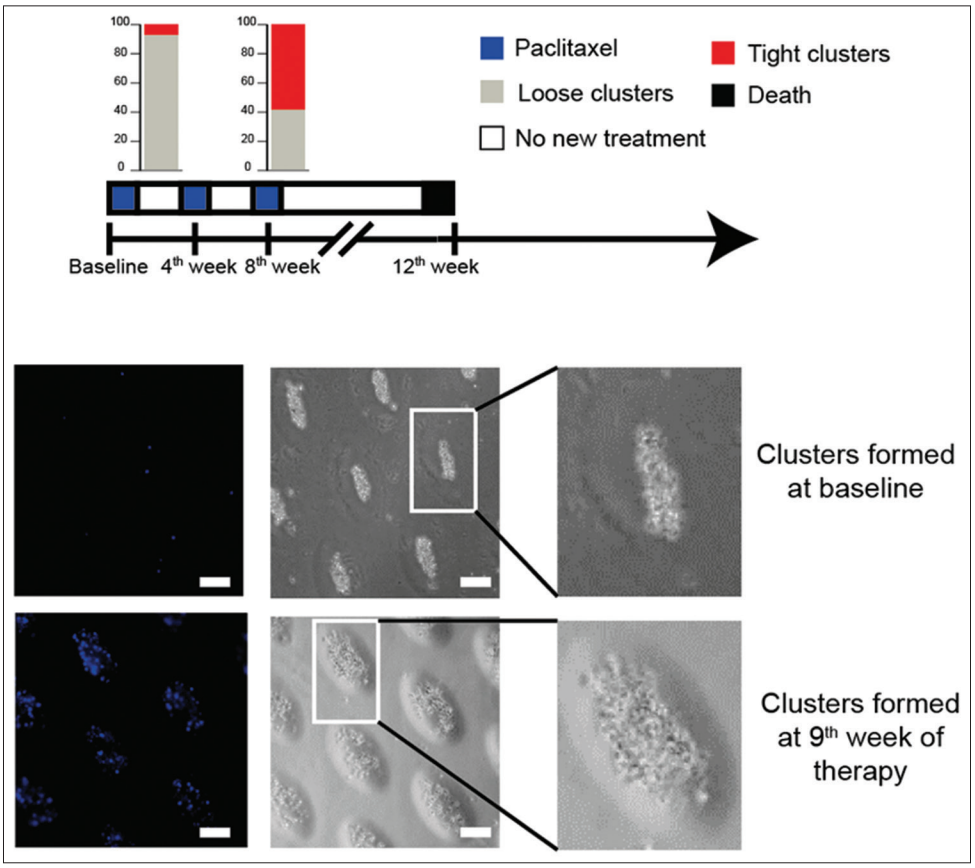

Figure 3: Nonresponder to paclitaxel in advanced breast cancer patient correlates to cluster formation

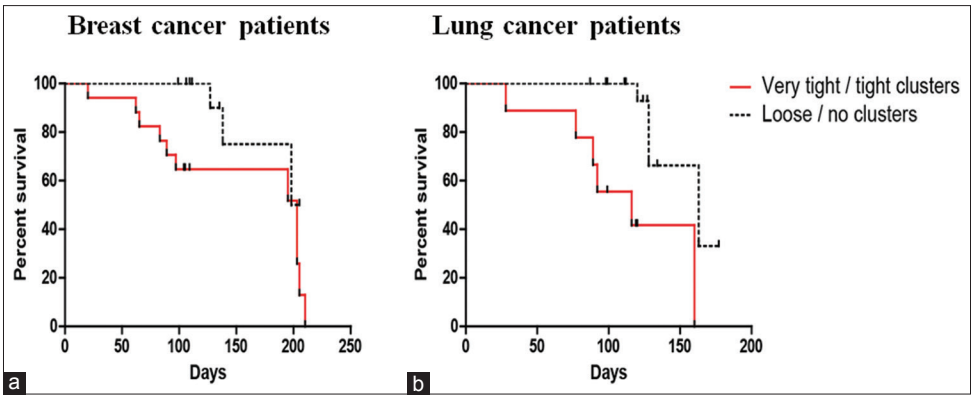

Figure 4: Correlation of survival in (a) Lung cancer (b) Breast cancer patients with formation of cluster formation of CTCç

were cultured in agar microwells following the set guidelines.

The CTCs formed clusters as they grew. Based on the rate of growth and the presumed adhesion qualities, they formed cell clusters. These clusters could be classified as very tight, tight, and loose using fluorescent intensity of 4'6-diamino-2-phenylindole stain [Figure 1].

We have been able to follow patients' progress and therapy response with serial CTC culturing and studying the cluster characteristics. The very tight clusters have shown to reflect poor responses to treatment. The tight clusters being replaced by tight or loose clusters on posttreatment follow-up cultures correlate with imaging confirmed responses very convincingly. Our initial two cohorts of metastatic breast and nonsmall cell lung cancer (NSCLC) show good correlation to this concept [Figures 2 and 3].

Although we started with NSCLC patients receiving combination chemotherapy, we took a bold step to look at Epidermal Growth Factor Receptor-mutated patients receiving tyrosine kinase inhibitors and also those patients receiving immune check point inhibitors. In both these groups, we were able to show the same correlation.

Although our cohorts are small, we have also demonstrated survival correlation with the tightness of the clusters [Figure 4].

This has encouraged us to continue our work further. We are in the process of looking at a similar project with other tumor types. Furthermore, we would like to involve more centers and clinicians in the future.

The next stage of our ongoing project is to look at drug sensitivity of these cultured CTCs to help guide therapy for our patients.

This has been an exciting time for me on this project and interacting with two other institutions and the researchers – collaborating with them and trying to understand different and interesting viewpoints.

I have learned a lot in this collaborative work and have got to visit the laboratories and see how all the CTC work is done and needs to be done in the future.

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