Background Tumor heterogeneity assessment may help predict response to immunotherapy. In melanoma mouse models, tumor heterogeneity impaired immune response. In addition, among lung cancer patients receiving immunotherapy, the high clonal neoantigen group had favorable survival and outcomes. Ideal methods of quantifying tumor heterogeneity are multiple biopsies or autopsy. However, these are not feasible in routine clinical practice. Circulating tumor DNA (ctDNA) is emerging as an alternative. Here, we reviewed the current state of tumor heterogeneity quantification from ctDNA. Furthermore, we propose a new tumor heterogeneity index (THI) based on our own scoring system, utilizing both ctDNA and tissue DNA.

Methods Systematic literature search on Pubmed was conducted up to August 18, 2020. A scoring system and THI were theoretically derived.

Results Two studies suggested their own methods of assessing tumor heterogeneity. One suggested clustering mutations with Pyclone, and the other suggested using the ratio of allele frequency (AF) to the maximum somatic allele frequency (MSAF). According to the former, the mutations in the highest cellular prevalence cluster can be defined as clonal mutations. According to the latter, the mutations with AF/MSAF<10% can be defined as subclonal mutations. To date, there have been no studies on utilizing both ctDNA and tissue DNA simultaneously to quantify tumor heterogeneity. We hypothesize that a mutation found in only one of either ctDNA or tissue DNA has a higher chance of being subclonal. We suggest a scoring system based on the previously mentioned methods to estimate the probability for a mutant allele to be subclonal. Adding up the points that correspond to the conditions results in a subclonality score (table 1). In a given ctDNA, the number of alleles with a subclonality score greater than or equal to 2 divided by the total number of alleles is defined as blood THI (bTHI) (figure 1). We can repeat the same calculation in a given tissue DNA for tissue THI (tTHI) (figure 2). Finally, we define composite THI (cTHI) as the mean of bTHI and tTHI.

Conclusions Tumor heterogeneity is becoming an important biomarker for predicting response to immunotherapy. Because autopsy and multiple biopsies are not feasible, utilizing both ctDNA and tissue DNA is the most comprehensive and practical approach. Therefore, we propose cTHI, for the first time, as a quantification measure of tumor heterogeneity.

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