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Optical Genome Mapping: a Novel Approach to Identifying Structural Variants in Metastatic Neuroendocrine Tumors

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BACKGROUND

Genomic structural variants (SVs) encompass a large portion of mutations driving cancer progression, however, there is a paucity of data regarding such drivers in metastatic neuroendocrine tumor (mNET). Existing studies have focused on short-read sequencing of primary NET samples, which can detect single nucleotide variants, but are unable to identify larger SVs. Such studies have demonstrated a low rate of genetic mutations. Optical genome mapping (OGM) represents a novel method of identifying longer sequence mutations, copy number variants (CNVs), and SVs, which may be missed by short-read technologies. This proof-of-concept study evaluated the use of OGM in mNET biopsy samples.

METHODS

Patients with hepatic mNET were enrolled in a prospective cohort study of the genetic profiling of NETs from June 2019 to March 2022. Image-guided biopsies were obtained from the dominant metastasis at the time of locoregional therapy. OGM was performed using the Bionano Saphyr chip (Bionano genomics, San Diego, CA, USA). SVs and CNVs were identified using Bionano statistical software. Genomic data was correlated with tumor grade and primary site and analyzed using descriptive statistics and the student's t test. The presence of chromothripsis, an inter-chromosomal translocation event accompanied by multiple CNV states, was evaluated for using shatterseek software.

RESULTS

Sixteen mNET samples were analyzed: 10 of small bowel origin (63%), 3 of pancreatic origin (19%), 2 of rectal origin (12%), and 1 of lung origin (6%). Three were grade 3 (19%), 12 were grade 2 (75%), and 1 was grade 1 (6%). A mean of 48 ± 43 and median of 32 (range 14-186) SVs were identified per sample. On average, deletions accounted for 44% of variants, insertions for 21%, inversions for 2%, inter-chromosomal translocations for 15%, and intra-chromosomal translocations for 18%. The mean number of SVs for grade 3 tumors was 100 ± 79 compared to 38 ± 20 for grade 2 tumors (p=0.27). The mean number of SVs for pancreatic mNETS was 113 ± 64 compared to 34 ± 20 for small bowel mNETs (p=0.13). Potential chromothripsis events were identified in 3 of pancreatic mNETs and 2 small bowel mNETs.

CONCLUSIONS

OGM was able to identify structural variants in all mNET samples. Trends towards differences between tumors of different grade and primary site of origin, as well as the presence of potential chromothripsis events, were observed in this small data set. An expanded study evaluating more samples and correlating genomic findings with clinical data and outcomes is ongoing.

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