Identification of somatic mutations in prostate adenocarcinoma with Gleason score 7 and 8 and their associations with biochemical recurrence

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Prostate cancer is a heterogeneous and multifocal disease. In general, it presents an indolent behavior, being asymptomatic in many cases. However, in some cases, the tumor rapidly progress to metastatic disease leading to patient death. The Gleason score (GS) is the main prognostic factor for localized disease and its classification is based on the sum of the primary and the secondary histological pattern, ranging from 2 to 10. Despite being the main classification method, GS alone does not provide accurate information about patient outcome, since patients with the same score can have different behaviors, particularly in intermediate GS (7-8). Therefore, in this study, we investigated genomic alterations in patients with intermediate GS that presented biochemical recurrence (BCR) compared to patients without recurrence, aiming to improve prognosis and also to reveal biological pathways involved with tumor aggressiveness. Thirty-two prostate adenocarcinoma patients with intermediate GS (7-8) that underwent radical prostatectomy at the A.C. Camargo Cancer Center, were selected and divided into 2 groups, 15 patients with and 17 patients without BCR, respectively. Using the TruSeq Custom Amplicon kit and the NextSeq platform (Illumina), we performed targeted-sequencing of 58 carefully selected genes, including 23 genes frequently mutated in prostate cancer and 35 genes mutated in other solid tumors, in 64 paired tumor/normal samples, generating ≥1000X average coverage per sample. Data were analyzed by the TruSeq Amplicon tool, which uses an aligner based on the Smith-Waterman algorithm and the "Somatic" variant caller. To identify somatic mutations, we compared tumor/normal samples using Varseq software and selected SNVs and Indels with a minimum coverage of 100X and a minimum allele frequency of 2% in the tumor, that leads to missense, nonsense, splice site or frameshift alterations. A total of 246 variants were identified, 161 SNVs and 85 Indels, with an average of 8 alterations per tumor (ranging from 0 to 41). Of the 58 genes investigated, 49 were affected in at least one patient (84.5%), suggesting that the custom panel is enriched in genes mutated in prostate cancer. Further analyzes are being conducted to evaluate the number and type of variants in the group of patients with and without BCR and to investigate which genes were preferentially affected and their related biological pathways. Therefore, we expect to obtain a profile of the genes most frequently mutated in prostate cancer and investigate possible associations with clinicopathological characteristics, to improve prognosis and better estimate the risk of recurrence.

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