**Table I: PCR primers used in this study**

|  |  |
| --- | --- |
| Exon | Primer sequence |
| 1A: Forward | 5’-CGC-GAA-GAC-TAC-GGA-GGT-3’ |
| 1A: Reverse | 5’-GGA-CTG-CGA-TTG-CAG-AAG-AT-3’ |
| 1B: Forward | 5’-GAG-TAC-GGC-CCT-GAA-GAA-GA-3’ |
| 1B: Reverse | 5’-GCT-TCA-GAC-CGT-GCT-ATC-GT-3’ |
| 2: Forward | 5’-CAC-CGG-TGT-GGC-TCT-TTA-AC-3’ |
| 2: Reverse | 5’-TGG-GCT-TAA-TTT-TTC-AAG-TGG-3’ |
| 3: Forward | 5’-GCA-AAG-CCT-CTT-GTT-CGT-TC-3’ |
| 3: Reverse | 5’-ACC-ATC-AAA-AGC-TGA-GAT-GAA-3’ |

**Table II: Characteristics of metastatic patients**

|  |  |
| --- | --- |
| Variables | Number of metastatic patients (%) |
| Metastatic sites |  |
| Lung | 32 (66.7%) |
| Bone | 27 (56.3%) |
| Distant lymph node | 16 (33.3%) |
| Liver | 7 (14.6%) |
| Unique site | 16 (33.3%) |
| MSKCC score |  |
| Favorable prognosis | 8 (16.7%) |
| Intermediate prognosis | 27 (56.3%) |
| Poor prognosis | 13 (27.0%) |
| Heng criteria |  |
| Favorable prognosis | 9 (18.7%) |
| Intermediate prognosis |  |
| Poor prognosis | 19 (39.6%) |
| Favorable prognosis | 20 (41.7%) |
| Treatment |  |
| Cytokines | 14 (29.2%) |
| Sunitinib (first-line or second line) | 13 (27.1%) |
| Sorafenib | 2 (7.1%) |
| Hormone therapy | 3 (10.7%) |
| Standard chemotherapy | 2 (7.1%) |
| Supportive care | 11 (39.3%) |
| Unknown | 8 (16.7%) |

**Table III: VHL complete status**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **N°** | **Mutation** | **Mutation type** | **Mutation site** | **cDNA change** | **Predicted protein change** | **Deletion** | **Promoter methylation** |
| 1 | YES | STOP | EXON 1 | c.208G>T | p.Glu70X | NO | NO |
| 2 | NO | NO MUTATION |  |  |  | YES | YES |
| 3 | YES | SPLICE SITE | EXON 3 | c.464-1G>C | Splicing effect | YES | NO |
| 4 | YES | FRAMESHIFT | EXON 2 | c.415del6insAACCCTA | p.Ser139AsnfsX5 | NO | NO |
| 5 | YES | FRAMESHIFT | EXON 3 | c.477delA | p.Glu160SerfsX10 | YES | NO |
| 6 | YES | MISSENSE | EXON 1 | c.277G>C | p.Gly93Arg | YES | NO |
| 7 | NO | NO MUTATION |  |  |  | YES | NO |
| 8 | YES | FRAMESHIFT | EXON 3 | c.504delT | p.Leu169GlnfsX32 | YES | NO |
| 9 | NO | NO MUTATION |  |  |  | YES | YES |
| 10 | YES | FRAMESHIFT | EXON 1 | c.186del14 | p.Arg64AlafsX63 | YES | NO |
| 11 | YES | SPLICE SITE | EXON 2 | c.463delG | splicing effect | YES | NO |
| 12 | NO | NO MUTATION |  |  |  | NO | NO |
| 13 | NO | NO MUTATION |  |  |  | YES | YES |
| 14 | YES | MISSENSE | EXON 3 | c.489A>C | p.Gln164Pro | YES | NO |
| 15 | NO | NO MUTATION |  |  |  | NO | NO |
| 16 | YES | FRAMESHIFT | EXON 2 | c.391delA | p.Asn131ThrfsX28 | YES | NO |
| 17 | YES | MISSENSE | EXON 1 | c.232A>T | p.Asn78Tyr | NO | NO |
| 18 | NO | NO MUTATION |  |  |  | YES | YES |
| 19 | YES | MISSENSE | EXON 2 | c.452T>G | p.Ile151Ser | NO | NO |
| 20 | YES | FRAMESHIFT | EXON 1 | c.230del5 | p.Cys77SerfsX53 | YES | NO |
| 21 | YES | FRAMESHIFT | EXON 3 | c.521delT | p.Tyr175ThrfsX27 | YES | NO |
| 22 | YES | STOP | EXON 3 | c.468T>G | p.Tyr156X | YES | NO |
| 23 | YES | STOP | EXON 2 | c.404T>A | p.Leu135X | NO | NO |
| 24 | YES | STOP | EXON 1 | c.194C>A | p.Ser65X | YES | NO |
| 25 | YES | FRAMESHIFT | EXON 2 | c.346del2 | p.Trp117AlafsX14 | YES | NO |
| 26 | YES | FRAMESHIFT | EXON 3 | c.528del6insC | p.ArgThr177fsX77 | YES | NO |
| 27 | NO | NO MUTATION |  |  |  | NO | NO |
| 28 | YES | MISSENSE | EXON 1 | c.194 C>G | p.Ser65Trp | YES | NO |
| 29 | YES | FRAMESHIFT | EXON 1 | c.279insGGAC | p.Glu94GlyfsX39 | NO | NO |
| 30 | YES | MISSENSE | EXON 1 | c.227T>C | p.Phe76Ser | YES | NO |
| 31 | YES | SPLICE SITE | EXON 2 | c.341-1G>A | Splicing effect | YES | NO |
| 32 | NO | NO MUTATION |  |  |  | NO | NO |
| 33 | YES | MISSENSE | EXON 2 | c.349 T>C | p.Trp117Arg | YES | NO |
| 34 | NO | NO MUTATION |  |  |  | NO | NO |
| 35 | YES | STOP | EXON 3 | c.479C>T | p.Arg161X | YES | NO |
| 36 | NO | NO MUTATION |  |  |  | YES | NO |
| 37 | YES | MISSENSE | EXON 1 | c.232A>C | p.Asn78His | YES | NO |
| 38 | NO | NO MUTATION |  |  |  | YES | YES |
| 39 | YES | STOP | EXON 3 | c.638C>T | p.Gln195X | YES | NO |
| 40 | NO | NO MUTATION |  |  |  | YES | YES |
| 41 | YES | FRAMESHIFT | EXON 1 | c.171del2insCCGGCCGGCC | p.Arg58ProfsX12 | NO | NO |
| 42 | YES | FRAMESHIFT | EXON 1 | c.261del2 | p.Trp88AlafsX43 | NO | NO |
| 43 | YES | STOP | EXON 1 | c.231C>A | p.Cys77X | YES | NO |
| 44 | NO | NO MUTATION |  |  |  | YES | NO |
| 45 | YES | FRAMESHIFT | EXON 1 | c.227del3 | p.Phe76del | YES | NO |
| 46 | YES | FRAMESHIFT | EXON 1 | c.286delC | p.Gln96SerfsX63 | YES | NO |
| 47 | NO | NO MUTATION |  |  |  | NO | NO |
| 48 | YES | MISSENSE | EXON 3 | c.473T>C | p.Leu158Pro | YES | NO |
| 49 | NO | NO MUTATION |  |  |  | YES | YES |
| 50 | YES | FRAMESHIFT | EXON 2 | c.407del2insG | p.Phe136TrpfsX23 | YES | NO |
| 51 | NO | NO MUTATION |  |  |  | YES | YES |
| 52 | NO | NO MUTATION |  |  |  | YES | YES |
| 53 | YES | SPLICE SITE | EXON 2 | c.463+1G>T | Splicing effect | YES | NO |
| 54 | NO | NO MUTATION |  |  |  | YES | NO |
| 55 | YES | FRAMESHIFT | EXON 1 | c.133del C | p.Ser72ProfsX87 | YES | NO |
| 56 | YES | MISSENSE | EXON 2 | c.463G>T | p.Val155Leu | YES | NO |
| 57 | YES | FRAMESHIFT | EXON 2 | c.343delC | p.His115ThrfsX44 | YES | NO |
| 58 | NO | NO MUTATION |  |  |  | YES | NO |
| 59 | YES | MISSENSE | EXON 1 | c.340G>C | p.Gly114Arg | YES | NO |
| 60 | YES | FRAMESHIFT | EXON 2 | c.404delT | p.Leu135TyrfsX24 | YES | NO |
| 61 | YES | MISSENSE | EXON 3 | c.484C>G | p.Cys162Trp | NO | NO |
| 62 | YES | FRAMESHIFT | EXON 1 | c.271delT | p.Phe91SerfsX68 | YES | NO |
| 63 | YES | FRAMESHIFT | EXON 2 | c.461delC | p.Pro154GlnfsX5 | YES | NO |
| 64 | YES | SPLICE SITE | EXON 2 | c.341-1G>T | Splicing effect | YES | NO |
| 65 | YES | STOP | EXON 1 | c.194C>A | p.Ser65X | YES | NO |
| 66 | YES | MISSENSE | EXON 2 | c.361G>T | p.Asp121Tyr | YES | NO |
| 67 | YES | FRAMESHIFT | EXON 2 | c.408insT | p.Val137CysfsX7 | YES | NO |
| 68 | NO | NO MUTATION |  |  |  | YES | YES |
| 69 | YES | FRAMESHIFT | EXON 1 | c.235dup3 | p.Asn78dup | YES | NO |
| 70 | YES | FRAMESHIFT | EXON 1 | c.300del2insT | p.Leu101CysfsX58 | YES | NO |
| 71 | YES | FRAMESHIFT | EXON 3 | c.469del9 | p.Thr157\_Leu158\_Lys159del | NO | NO |
| 72 | YES | FRAMESHIFT | EXON 2 | c.393del2insT | p.Gln132LysfsX27 | NO | NO |
| 73 | YES | STOP | EXON 1 | c.208G>T | p.Glu70X | YES | NO |
| 74 | YES | FRAMESHIFT | EXON 3 | c.515delC | p.Pro172LeufsX30 | YES | NO |
| 75 | YES | MISSENSE | EXON 2 | c.436C>G | p.Pro146Ala | NO | NO |
| 76 | YES | FRAMESHIFT | EXON 3 | c.493insT | p.Val166CysfsX8 | YES | NO |
| 77 | NO | NO MUTATION |  |  |  | YES | YES |
| 78 | YES | FRAMESHIFT | EXON 2 | c.449delA | p.Asn150IlefsX9 | YES | NO |
| 79 | NO | NO MUTATION |  |  |  | NO | NO |
| 80 | NO | NO MUTATION |  |  |  | NO | YES |
| 81 | YES | FRAMESHIFT | EXON 2 | c.423delT | p.Asn141LysfsX18 | YES | NO |
| 82 | YES | FRAMESHIFT | EXON 2 | c.454delA | p.Thr152HisfsX7 | YES | NO |
| 83 | NO | NO MUTATION |  |  |  | NO | NO |
| 84 | NO | NO MUTATION |  |  |  | NO | NO |
| 85 | NO | NO MUTATION |  |  |  | NO | NO |
| 86 | YES | FRAMESHIFT | EXON 1 | c.234delT | p.Arg79AlafsX79 | NO | NO |
| 87 | YES | FRAMESHIFT | EXON 1 | c.242delC | p.Pro81ArgfsX78 | YES | NO |
| 88 | YES | FRAMESHIFT | EXON 2 | c.404delT | p.Leu135TyrfsX24 | YES | NO |
| 89 | NO | NO MUTATION |  |  |  | YES | YES |
| 90 | YES | MISSENSE | EXON 1 | c.240T>A | p.Ser80Arg | YES | NO |
| 91 | YES | MISSENSE | EXON 2 | c.343C>A | p.His115Asn | YES | NO |
| 92 | YES | MISSENSE | EXON 2 | c.343C>A | p.His115Asn | YES | NO |
| 93 | YES | MISSENSE | EXON 1 | c.240T>G | p.Ser80Arg | YES | NO |
| 94 | YES | STOP | EXON 1 | c.208G>T | p.Glu70X | YES | NO |
| 95 | YES | MISSENSE | EXON 1 | c.264G>C | p.Trp88Cys | YES | NO |
| 96 | YES | SPLICE SITE | EXON 2 | c.463+2T>C | Splicing effect | YES | NO |
| 97 | NO | NO MUTATION |  |  |  | YES | NO |
| 98 | NO | NO MUTATION |  |  |  | NO | NO |