**Supplemental Table 1:** Patient Characteristics for ccRCC Multi-stage Tumor Microarray (tissue set 1) used in the study.

|  | | TMA Block | | | |
| --- | --- | --- | --- | --- | --- |
|  | All | RCC1 | RCC2 | RCC3 | RCC4 |
| **Patient Characteristics** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| **All** | **380 (100%)** | **90 (100%)** | **95 (100%)** | **110 (100%)** | **85 (100%)** |
| Age at Surgery - median(min,max) | | | | | |
| N=380 | 58.9  (25.7, 84.2) | 59.0  (30.8, 79.3) | 58.1  (25.7, 84.2) | 61.8  (38.3, 78.6) | 57.7  (39.6, 82.6) |
| Gender | | | | | |
| Female | 119 (31%) | 33 (37%) | 28 (29%) | 35 (32%) | 23 (27%) |
| Male | 261 (69%) | 57 (63%) | 67 (71%) | 75 (68%) | 62 (73%) |
| Race/Ethnicity | | | | | |
| White | 284 (75%) | 61 (68%) | 71 (75%) | 79 (72%) | 73 (86%) |
| Black | 21 (6%) | 6 (7%) | 8 (8%) | 6 (5%) | 1 (1%) |
| Hispanic | 63 (17%) | 19 (21%) | 15 (16%) | 21 (19%) | 8 (9%) |
| Other | 12 (3%) | 4 (4%) | 1 (1%) | 4 (4%) | 3 (4%) |
| ECOG at Surgery | | | | | |
| 0 | 280 (74%) | 73 (81%) | 66 (69%) | 93 (85%) | 48 (56%) |
| >=1 | 100 (26%) | 17 (19%) | 29 (31%) | 17 (15%) | 37 (44%) |
| Clinical T Stage | | | | | |
| T1 | 115 (30%) | 87 (97%) | 11 (12%) | 0 (0%) | 17 (20%) |
| T2 | 95 (25%) | 2 (2%) | 81 (85%) | 1 (1%) | 11 (13%) |
| T3 | 166 (44%) | 1 (1%) | 3 (3%) | 109 (99%) | 53 (62%) |
| T4 | 4 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 (5%) |
| Clinical M Stage | | | | | |
| Yes | 87 (23%) | 2 (2%) | 3 (3%) | 2 (2%) | 80 (94%) |
| No | 293 (77%) | 88 (98%) | 92 (97%) | 108 (98%) | 5 (6%) |
| Tumor Grade\* | | | | | |
| 1 | 3 (1%) | 3 (3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 2 | 104 (27%) | 45 (50%) | 25 (26%) | 23 (21%) | 11 (13%) |
| 3 | 197 (52%) | 37 (41%) | 56 (59%) | 67 (61%) | 37 (44%) |
| 4 | 75 (20%) | 5 (6%) | 14 (15%) | 19 (17%) | 37 (44%) |
| Tumor Size (cm) - median (Q1, Q3) | | | | | |
| N=85 | 9.0 (7.0, 11.4) | 4.2 (3.0, 5.0) | 8.9 (7.8, 10.5) | 9.0 (6.3, 11.0) | 9.0 (7.0, 11.4) |
| LVI | | | | | |
| Yes | 32 (8%) | 4 (4%) | 4 (4%) | 10 (9%) | 14 (16%) |
| No | 348 (92%) | 86 (96%) | 91 (96%) | 100 (91%) | 71 (84%) |
| Necrosis\* | | | | | |
| Yes | 157 (41%) | 14 (16%) | 44 (46%) | 53 (48%) | 46 (54%) |
| No | 222 (58%) | 76 (84%) | 51 (54%) | 56 (51%) | 39 (46%) |
| Cystic Areas\* | | | | | |
| Yes | 66 (17%) | 17 (19%) | 22 (23%) | 14 (13%) | 13 (15%) |
| No | 313 (82%) | 73 (81%) | 73 (77%) | 95 (86%) | 72 (85%) |

**Supplemental Table 2A**: HIF-1α (total) Levels within Patients by Clinical Characteristics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient Characteristics** | **Within Patient HIF-1α (total) Values** | | | | | |
| **Median** | | **Mean** | | **SE** | |
| **Median (IQR)** | **P-value** | **Median (IQR)** | **P-value** | **Median (IQR)** | **P-value** |
| **All** | **0.025 (0.012, 0.052)** |  | **0.026 (0.014, 0.053)** |  | **0.007 (0.003, 0.017)** |  |
| Age | | | | | | |
| <50 | 0.025 (0.012, 0.055) | 0.56 | 0.027 (0.014, 0.058) | 0.79 | 0.006 (0.003, 0.018) | 0.75 |
| 50-64 | 0.025 (0.012, 0.056) |  | 0.026 (0.014, 0.054) |  | 0.008 (0.003, 0.016) |  |
| >=65 | 0.022 (0.012, 0.041) |  | 0.027 (0.013, 0.048) |  | 0.006 (0.003, 0.017) |  |
| Gender | | | | | | |
| Male | 0.025 (0.012, 0.053) | 0.59 | 0.027 (0.014, 0.054) | 0.32 | 0.008 (0.004, 0.019) | **0.01** |
| Female | 0.023 (0.013, 0.043) |  | 0.023 (0.013, 0.046) |  | 0.005 (0.003, 0.013) |  |
| Race/Ethnicity | | | | | | |
| White | 0.027 (0.013, 0.056) | **0.02** | 0.030 (0.014, 0.055) | **0.02** | 0.008 (0.003, 0.018) | 0.42 |
| Black | 0.012 (0.009, 0.032) |  | 0.014 (0.010, 0.034) |  | 0.004 (0.003, 0.013) |  |
| Hispanic | 0.020 (0.012, 0.038) |  | 0.021 (0.014, 0.038) |  | 0.005 (0.003, 0.014) |  |
| Other | 0.023 (0.012, 0.052) |  | 0.023 (0.015, 0.059) |  | 0.007 (0.003, 0.009) |  |
| ECOG at Surgery | | | | | | |
| 0 | 0.023 (0.012, 0.049) | 0.74 | 0.026 (0.014, 0.049) | 0.79 | 0.007 (0.003, 0.016) | 0.7 |
| >=1 | 0.027 (0.011, 0.064) |  | 0.027 (0.013, 0.064) |  | 0.008 (0.003, 0.021) |  |
| T Stage | | | | | | |
| T1 | 0.028 (0.014, 0.050) | **0.003** | 0.028 (0.014, 0.049) | **0.005** | 0.007 (0.003, 0.013) | **0.01** |
| T2 | 0.039 (0.015, 0.064) |  | 0.040 (0.017, 0.067) |  | 0.013 (0.004, 0.023) |  |
| T3 | 0.019 (0.011, 0.037) |  | 0.020 (0.012, 0.043) |  | 0.006 (0.003, 0.014) |  |
| T4 | 0.051 (0.015, 0.107) |  | 0.055 (0.016, 0.109) |  | 0.019 (0.004, 0.027) |  |
| M Stage | | | | | | |
| No | 0.021 (0.012, 0.049) | **0.01** | 0.024 (0.013, 0.049) | **0.02** | 0.006 (0.003, 0.016) | **0.02** |
| Yes | 0.032 (0.017, 0.066) |  | 0.033 (0.018, 0.062) |  | 0.009 (0.004, 0.024) |  |
| Tumor Grade | | | | | | |
| 1 | 0.015 (0.007, 0.153) | **0.05** | 0.020 (0.007, 0.153) | **0.04** | 0.005 (0.002, 0.008) | **0.01** |
| 2 | 0.021 (0.011, 0.050) |  | 0.022 (0.012, 0.048) |  | 0.005 (0.003, 0.013) |  |
| 3 | 0.022 (0.012, 0.049) |  | 0.025 (0.014, 0.051) |  | 0.007 (0.003, 0.016) |  |
| 4 | 0.033 (0.017, 0.066) |  | 0.035 (0.019, 0.066) |  | 0.011 (0.004, 0.023) |  |
| Tumor Size | | | | | | |
| <5 cm | 0.025 (0.012, 0.052) | 0.11 | 0.024 (0.013, 0.053) | 0.16 | 0.006 (0.002, 0.013) | 0.06 |
| 5-<10 cm | 0.021 (0.011, 0.046) |  | 0.025 (0.012, 0.049) |  | 0.007 (0.003, 0.014) |  |
| >=10 cm | 0.029 (0.014, 0.064) |  | 0.032 (0.015, 0.067) |  | 0.009 (0.004, 0.023) |  |
| LVI | | | | | | |
| No | 0.023 (0.012, 0.053) | 0.53 | 0.026 (0.013, 0.053) | 0.48 | 0.007 (0.003, 0.017) | 0.25 |
| Yes | 0.026 (0.017, 0.045) |  | 0.028 (0.019, 0.046) |  | 0.009 (0.004, 0.019) |  |
| Necrosis | | | | | | |
| No | 0.023 (0.013, 0.050) | 0.73 | 0.024 (0.014, 0.049) | 0.28 | 0.007 (0.003, 0.013) | **0.05** |
| Yes | 0.025 (0.011, 0.057) |  | 0.030 (0.013, 0.058) |  | 0.008 (0.003, 0.022) |  |
| Cystic Areas | | | | | | |
| No | 0.025 (0.012, 0.049) | 0.66 | 0.025 (0.014, 0.049) | 0.49 | 0.007 (0.003, 0.016) | 0.14 |
| Yes | 0.025 (0.011, 0.068) |  | 0.031 (0.012, 0.067) |  | 0.011 (0.004, 0.023) |  |

**Supplemental Table 2B**: HIF-2α Levels within Patients by Patient and Tumor Characteristics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient Characteristics** | **Within Patient HIF-2α Values** | | | | | |
| **Median** | | **Mean** | | **SE** | |
| **Median (IQR)** | **P-value** | **Median (IQR)** | **P-value** | **Median (IQR)** | **P-value** |
| **All** | **0.183 (0.064, 0.383)** |  | **0.192 (0.067, 0.386)** |  | **0.037 (0.017, 0.072)** |  |
| Age | | | | | | |
| <50 | 0.166 (0.058, 0.348) | 0.61 | 0.167 (0.066, 0.358) | 0.74 | 0.038 (0.022, 0.073) | 0.33 |
| 50-64 | 0.204 (0.063, 0.422) |  | 0.210 (0.066, 0.409) |  | 0.034 (0.017, 0.074) |  |
| >=65 | 0.162 (0.065, 0.350) |  | 0.176 (0.069, 0.353) |  | 0.036 (0.015, 0.060) |  |
| Gender | | | | | | |
| Male | 0.180 (0.056, 0.398) | 0.75 | 0.205 (0.065, 0.398) | 0.75 | 0.037 (0.017, 0.068) | 0.82 |
| Female | 0.187 (0.073, 0.333) |  | 0.187 (0.087, 0.335) |  | 0.035 (0.016, 0.076) |  |
| Race/Ethnicity | | | | | | |
| Black | 0.113 (0.044, 0.319) |  | 0.114 (0.045, 0.317) |  | 0.031 (0.014, 0.058) |  |
| Hispanic | 0.160 (0.050, 0.335) |  | 0.181 (0.056, 0.364) |  | 0.031 (0.014, 0.075) |  |
| Other | 0.245 (0.064, 0.514) |  | 0.245 (0.064, 0.594) |  | 0.037 (0.020, 0.067) |  |
| White | 0.190 (0.073, 0.398) | 0.34 | 0.199 (0.081, 0.395) | 0.4 | 0.038 (0.018, 0.073) | 0.69 |
| ECOG at Surgery | | | | | | |
| 0 | 0.200 (0.066, 0.420) | **0.04** | 0.225 (0.074, 0.420) | **0.03** | 0.038 (0.017, 0.075) | 0.38 |
| >=1 | 0.146 (0.051, 0.308) |  | 0.159 (0.061, 0.308) |  | 0.035 (0.018, 0.062) |  |
| T Stage | | | | | | |
| T1 | 0.415 (0.214, 0.581) | **<0.001** | 0.419 (0.240, 0.593) | **<0.001** | 0.065 (0.032, 0.096) | **<0.001** |
| T2 | 0.193 (0.087, 0.272) |  | 0.195 (0.094, 0.314) |  | 0.034 (0.017, 0.061) |  |
| T3 | 0.090 (0.036, 0.227) |  | 0.099 (0.046, 0.245) |  | 0.025 (0.014, 0.047) |  |
| T4 | 0.190 (0.168, 0.212) |  | 0.166 (0.154, 0.179) |  | 0.052 (0.051, 0.052) |  |
| M Stage | | | | | | |
| No | 0.196 (0.067, 0.419) | **0.01** | 0.219 (0.081, 0.419) | **0.01** | 0.037 (0.017, 0.074) | 0.37 |
| Yes | 0.146 (0.041, 0.276) |  | 0.137 (0.052, 0.276) |  | 0.032 (0.018, 0.064) |  |
| Tumor Grade | | | | | | |
| 1 | 0.448 (0.141, 0.755) | **0.02** | 0.473 (0.191, 0.755) | **0.01** | 0.068 (0.068, 0.068) | 0.64 |
| 2 | 0.235 (0.110, 0.425) |  | 0.245 (0.111, 0.444) |  | 0.038 (0.018, 0.074) |  |
| 3 | 0.179 (0.062, 0.415) |  | 0.188 (0.066, 0.415) |  | 0.037 (0.017, 0.072) |  |
| 4 | 0.115 (0.049, 0.264) |  | 0.121 (0.052, 0.262) |  | 0.031 (0.015, 0.065) |  |
| Tumor Size | | | | | | |
| <5 cm | 0.389 (0.155, 0.581) | **<0.001** | 0.410 (0.191, 0.581) | **<0.001** | 0.048 (0.025, 0.088) | **0.02** |
| 5-<10 cm | 0.166 (0.057, 0.375) |  | 0.168 (0.064, 0.369) |  | 0.036 (0.015, 0.071) |  |
| >=10 cm | 0.146 (0.052, 0.255) |  | 0.155 (0.063, 0.262) |  | 0.031 (0.016, 0.061) |  |
| LVI | | | | | | |
| No | 0.189 (0.064, 0.403) | 0.14 | 0.202 (0.068, 0.401) | 0.08 | 0.038 (0.017, 0.074) | 0.06 |
| Yes | 0.115 (0.060, 0.256) |  | 0.116 (0.062, 0.256) |  | 0.022 (0.013, 0.044) |  |
| Necrosis | | | | | | |
| No | 0.233 (0.087, 0.438) | **0.001** | 0.238 (0.095, 0.438) | **0.001** | 0.037 (0.017, 0.072) | 0.87 |
| Yes | 0.145 (0.053, 0.272) |  | 0.151 (0.061, 0.311) |  | 0.036 (0.017, 0.068) |  |
| Cystic Areas | | | | | | |
| No | 0.187 (0.064, 0.393) | 0.81 | 0.191 (0.066, 0.393) | 0.77 | 0.038 (0.017, 0.071) | 0.53 |
| Yes | 0.177 (0.057, 0.360) |  | 0.205 (0.067, 0.355) |  | 0.032 (0.014, 0.075) |  |

**Supplemental Table 2C:** HAF Levels within Patients by Clinical Characteristics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient Characteristics** | **Within Patient HAF Values** | | | | | |
| **Median** | | **Mean** | | **SE** | |
| **Median (IQR)** | **P-value** | **Median (IQR)** | **P-value** | **Median (IQR)** | **P-value** |
| **All** | **0.085 (0.011, 0.235)** |  | **0.095 (0.013, 0.240)** |  | **0.023 (0.005, 0.049)** |  |
| Age |  |  |  |  |  |  |
| <50 | 0.113 (0.010, 0.248) | 0.67 | 0.114 (0.013, 0.265) | 0.57 | 0.016 (0.004, 0.045) | 0.06 |
| 50-64 | 0.091 (0.018, 0.220) |  | 0.097 (0.021, 0.224) |  | 0.028 (0.007, 0.061) |  |
| >=65 | 0.063 (0.007, 0.249) |  | 0.079 (0.007, 0.240) |  | 0.021 (0.003, 0.043) |  |
| Gender | | | | | | |
| Male | 0.063 (0.009, 0.208) | **0.01** | 0.067 (0.012, 0.211) | **0.02** | 0.021 (0.004, 0.047) | 0.28 |
| Female | 0.131 (0.018, 0.267) |  | 0.132 (0.021, 0.267) |  | 0.029 (0.007, 0.054) |  |
| Race/Ethnicity | | | | | | |
| White | 0.097 (0.013, 0.228) | 0.65 | 0.099 (0.017, 0.240) | 0.62 | 0.026 (0.006, 0.049) | 0.33 |
| Black | 0.108 (0.033, 0.229) |  | 0.108 (0.035, 0.229) |  | 0.027 (0.009, 0.071) |  |
| Hispanic | 0.038 (0.008, 0.253) |  | 0.043 (0.008, 0.264) |  | 0.016 (0.003, 0.044) |  |
| Other | 0.100 (0.006, 0.294) |  | 0.100 (0.009, 0.282) |  | 0.009 (0.002, 0.053) |  |
| ECOG at Surgery | | | | | | |
| 0 | 0.094 (0.014, 0.228) | 0.39 | 0.096 (0.016, 0.240) | 0.5 | 0.021 (0.005, 0.050) | 0.8 |
| >=1 | 0.072 (0.009, 0.241) |  | 0.081 (0.010, 0.233) |  | 0.027 (0.004, 0.047) |  |
| T Stage | | | | | | |
| T1 | 0.153 (0.024, 0.300) | **<0.001**. | 0.164 (0.034, 0.300) | **<0.001**. | 0.029 (0.005, 0.048) | 0.25 |
| T2 | 0.107 (0.014, 0.273) |  | 0.112 (0.021, 0.282) |  | 0.026 (0.006, 0.054) |  |
| T3 | 0.048 (0.006, 0.169) |  | 0.055 (0.007, 0.171) |  | 0.019 (0.003, 0.047) |  |
| T4 | 0.003 (0.001, 0.118) |  | 0.012 (0.002, 0.118) |  | 0.004 (0.002, 0.011) |  |
| M Stage | | | | | | |
| No | 0.109 (0.014, 0.264) | . **<0.001** | 0.113 (0.014, 0.267) | **0.001** | 0.027 (0.006, 0.052) | 0.18 |
| Yes | 0.033 (0.006, 0.130) |  | 0.049 (0.009, 0.130) |  | 0.017 (0.003, 0.044) |  |
| Tumor Grad | | | | | | |
| 1 | 0.202 (0.003, 0.487) | **<0.001**. | 0.210 (0.003, 0.487) | . **<0.001** | 0.024 (0.002, 0.047) | 0.14 |
| 2 | 0.146 (0.024, 0.310) |  | 0.167 (0.043, 0.308) |  | 0.031 (0.008, 0.052) |  |
| 3 | 0.100 (0.010, 0.218) |  | 0.104 (0.014, 0.214) |  | 0.024 (0.005, 0.051) |  |
| 4 | 0.027 (0.005, 0.127) |  | 0.038 (0.006, 0.129) |  | 0.015 (0.003, 0.038) |  |
| Tumor Size | | | | | | |
| <5 cm | 0.161 (0.030, 0.291) | **0.02** | 0.169 (0.032, 0.292) | **0.02** | 0.029 (0.008, 0.053) | 0.18 |
| 5-<10 cm | 0.065 (0.009, 0.221) |  | 0.076 (0.010, 0.214) |  | 0.018 (0.003, 0.045) |  |
| >=10 cm | 0.065 (0.013, 0.201) |  | 0.079 (0.013, 0.199) |  | 0.027 (0.006, 0.062) |  |
| LVI | | | | | | |
| No | 0.097 (0.013, 0.237) | **0.02** | 0.108 (0.016, 0.241) | **0.02** | 0.026 (0.005, 0.051) | 0.11 |
| Yes | 0.022 (0.004, 0.189) |  | 0.035 (0.004, 0.178) |  | 0.018 (0.001, 0.039) |  |
| Necrosis | | | | | | |
| No | 0.106 (0.012, 0.263) | 0.15 | 0.110 (0.013, 0.265) | 0.27 | 0.022 (0.003, 0.047) | 0.41 |
| Yes | 0.063 (0.010, 0.211) |  | 0.069 (0.014, 0.223) |  | 0.024 (0.006, 0.051) |  |
| Cystic Areas | | | | | | |
| No | 0.068 (0.009, 0.224) | **0.04** | 0.081 (0.011, 0.228) | **0.04** | 0.022 (0.003, 0.050) | 0.2 |
| Yes | 0.135 (0.030, 0.239) |  | 0.135 (0.042, 0.245) |  | 0.027 (0.011, 0.047) |  |

**Supplemental Table 2D**: HIF-1α (stroma) Levels within Patients by Clinical Characteristics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient Characteristics** | **Within Patient HAF Values** | | | | | |
| **Median** | | **Mean** | | **SE** | |
| **Median (IQR)** | **P-value** | **Median (IQR)** | **P-value** | **Median (IQR)** | **P-value** |
| **All** | **0.085 (0.011, 0.235)** |  | **0.095 (0.013, 0.240)** |  | **0.023 (0.005, 0.049)** |  |
| Age |  |  |  |  |  |  |
| <50 | 0.113 (0.010, 0.248) | 0.67 | 0.114 (0.013, 0.265) | 0.57 | 0.016 (0.004, 0.045) | 0.06 |
| 50-64 | 0.091 (0.018, 0.220) |  | 0.097 (0.021, 0.224) |  | 0.028 (0.007, 0.061) |  |
| >=65 | 0.063 (0.007, 0.249) |  | 0.079 (0.007, 0.240) |  | 0.021 (0.003, 0.043) |  |
| Gender | | | | | | |
| Male | 0.063 (0.009, 0.208) | **0.01** | 0.067 (0.012, 0.211) | **0.02** | 0.021 (0.004, 0.047) | 0.28 |
| Female | 0.131 (0.018, 0.267) |  | 0.132 (0.021, 0.267) |  | 0.029 (0.007, 0.054) |  |
| Race/Ethnicity | | | | | | |
| White | 0.097 (0.013, 0.228) | 0.65 | 0.099 (0.017, 0.240) | 0.62 | 0.026 (0.006, 0.049) | 0.33 |
| Black | 0.108 (0.033, 0.229) |  | 0.108 (0.035, 0.229) |  | 0.027 (0.009, 0.071) |  |
| Hispanic | 0.038 (0.008, 0.253) |  | 0.043 (0.008, 0.264) |  | 0.016 (0.003, 0.044) |  |
| Other | 0.100 (0.006, 0.294) |  | 0.100 (0.009, 0.282) |  | 0.009 (0.002, 0.053) |  |
| ECOG at Surgery | | | | | | |
| 0 | 0.094 (0.014, 0.228) | 0.39 | 0.096 (0.016, 0.240) | 0.5 | 0.021 (0.005, 0.050) | 0.8 |
| >=1 | 0.072 (0.009, 0.241) |  | 0.081 (0.010, 0.233) |  | 0.027 (0.004, 0.047) |  |
| T Stage | | | | | | |
| T1 | 0.153 (0.024, 0.300) | **<0.001**. | 0.164 (0.034, 0.300) | **<0.001**. | 0.029 (0.005, 0.048) | 0.25 |
| T2 | 0.107 (0.014, 0.273) |  | 0.112 (0.021, 0.282) |  | 0.026 (0.006, 0.054) |  |
| T3 | 0.048 (0.006, 0.169) |  | 0.055 (0.007, 0.171) |  | 0.019 (0.003, 0.047) |  |
| T4 | 0.003 (0.001, 0.118) |  | 0.012 (0.002, 0.118) |  | 0.004 (0.002, 0.011) |  |
| M Stage | | | | | | |
| No | 0.109 (0.014, 0.264) | . **<0.001** | 0.113 (0.014, 0.267) | **0.001** | 0.027 (0.006, 0.052) | 0.18 |
| Yes | 0.033 (0.006, 0.130) |  | 0.049 (0.009, 0.130) |  | 0.017 (0.003, 0.044) |  |
| Tumor Grad | | | | | | |
| 1 | 0.202 (0.003, 0.487) | **<0.001**. | 0.210 (0.003, 0.487) | . **<0.001** | 0.024 (0.002, 0.047) | 0.14 |
| 2 | 0.146 (0.024, 0.310) |  | 0.167 (0.043, 0.308) |  | 0.031 (0.008, 0.052) |  |
| 3 | 0.100 (0.010, 0.218) |  | 0.104 (0.014, 0.214) |  | 0.024 (0.005, 0.051) |  |
| 4 | 0.027 (0.005, 0.127) |  | 0.038 (0.006, 0.129) |  | 0.015 (0.003, 0.038) |  |
| Tumor Size | | | | | | |
| <5 cm | 0.161 (0.030, 0.291) | **0.02** | 0.169 (0.032, 0.292) | **0.02** | 0.029 (0.008, 0.053) | 0.18 |
| 5-<10 cm | 0.065 (0.009, 0.221) |  | 0.076 (0.010, 0.214) |  | 0.018 (0.003, 0.045) |  |
| >=10 cm | 0.065 (0.013, 0.201) |  | 0.079 (0.013, 0.199) |  | 0.027 (0.006, 0.062) |  |
| LVI | | | | | | |
| No | 0.097 (0.013, 0.237) | **0.02** | 0.108 (0.016, 0.241) | **0.02** | 0.026 (0.005, 0.051) | 0.11 |
| Yes | 0.022 (0.004, 0.189) |  | 0.035 (0.004, 0.178) |  | 0.018 (0.001, 0.039) |  |
| Necrosis | | | | | | |
| No | 0.106 (0.012, 0.263) | 0.15 | 0.110 (0.013, 0.265) | 0.27 | 0.022 (0.003, 0.047) | 0.41 |
| Yes | 0.063 (0.010, 0.211) |  | 0.069 (0.014, 0.223) |  | 0.024 (0.006, 0.051) |  |
| Cystic Areas | | | | | | |
| No | 0.068 (0.009, 0.224) | **0.04** | 0.081 (0.011, 0.228) | **0.04** | 0.022 (0.003, 0.050) | 0.2 |
| Yes | 0.135 (0.030, 0.239) |  | 0.135 (0.042, 0.245) |  | 0.027 (0.011, 0.047) |  |

**Supplemental Table 3** Overall Survival by Patient Characteristics.

|  | | **Overall Survival** | | |
| --- | --- | --- | --- | --- |
| **Patient Characteristic** |  | **Deaths/N** | **5-Year (SD)** | **P-Value** |
| **All Patients** |  | **195/380** | **66.7% (2.5%)** |  |
| Age\* |  |  |  | **<0.001** |
| 50-64 | 88/174 | 62.7% (3.7%) |  |
| <50 | 29/81 | 73.0% (5.0%) |  |
| >=65 | 78/125 | 68.4% (4.3%) |  |
| Gender |  |  |  | 0.73 |
| Female | 61/119 | 67.8% (4.4%) |  |
| Male | 134/261 | 66.3% (3.0%) |  |
| Race/Ethnicity |  |  |  | 0.32 |
| White | 156/284 | 64.5% (2.9%) |  |
| Black | 9/21 | 71.4% (9.9%) |  |
| Hispanic | 25/63 | 74.7% (5.7%) |  |
| Other | 5/12 | 72.7% (13.4%) |  |
| Clinical T Stage |  |  |  | **<0.001** |
| T1 | 52/115 | 77.9% (3.9%) |  |
| T2 | 40/95 | 76.7% (4.5%) |  |
| T3 | 100/166 | 53.6% (4.0%) |  |
| T4 | 3/4 | 50.0% (25.0%) |  |
| Clinical M Stage |  |  |  | **<0.001** |
| No | 121/293 | 78.1% (2.5%) |  |
| Yes | 74/87 | 28.5% (4.9%) |  |
| Tumor Grade |  |  |  | **<0.001** |
| 1 | 3/3 | 100.0% (0.0%) |  |
| 2 | 45/104 | 75.4% (4.3%) |  |
| 3 | 94/197 | 71.9% (3.3%) |  |
| 4 | 53/75 | 39.3% (5.8%) |  |
| Tumor Size\* |  |  |  | **<0.001** |
| 5-<10 cm | 92/184 | 67.1% (3.5%) |  |
| <5 cm | 29/74 | 80.8% (4.6%) |  |
| >=10 cm | 74/122 | 57.5% (4.6%) |  |
| LVI |  |  |  | **0.01** |
| No | 173/348 | 68.4% (2.5%) |  |
| Yes | 22/32 | 49.6% (8.9%) |  |
| Necrosis |  |  |  | **0.001** |
| No | 106/222 | 72.8% (3.0%) |  |
| Yes | 88/157 | 57.8% (4.0%) |  |
| Cystic Areas |  |  |  | 0.66 |
| No | 158/313 | 67.0% (2.7%) |  |
| Yes | 36/66 | 65.0% (5.9%) |  |
| HAF Mean\* |  |  |  | **0.02** |
| <0.14 | 133/229 | 61.0% (3.3%) |  |
| >=0.14 | 59/146 | 75.3% (3.6%) |  |
| HIF-2α Mean\* |  |  |  | **<0.001** |
|  | <0.102 | 60/117 | 60.5% (4.7%) |  |
|  | 0.102-<0.307 | 69/120 | 57.8% (4.6%) |  |
|  | >=0.307 | 51/119 | 79.6% (3.7%) |  |
| HIF-1α (total) Mean\* |  |  |  | **0.02** |
| <0.0171 | 57/124 | 71.8% (4.1%) |  |
| 0.0171-<0.041 | 63/122 | 66.0% (4.4%) |  |
| >=0.041 | 70/124 | 61.1% (4.4%) |  |
| HIF-1α (Stroma) Mean\* |  |  |  | **0.02** |
| <0.005 | 55/116 | 74.4% (4.1%) |  |
| 0.005-<0.014 | 65/135 | 66.6% (4.1%) |  |
| >=0.014 | 71/120 | 57.8% (4.6%) |  |

\*These variables are continuous measures. The p-value is based on the continuous variable, and the groupings are used for presentation of time estimates only.

**Supplemental Table 4.** Progression-Free survival by Patient Characteristics

|  | | **PFS** | | |
| --- | --- | --- | --- | --- |
| **Patient Characteristic** |  | **Events/N** | **5-Year (SD)** | **P-Value** |
| **All Patients** |  | **206/378** | **50.3% (2.7%)** |  |
| Age\* |  |  |  | 0.30 |
| 50-64 | 97/173 | 48.0% (3.9%) |  |
| <50 | 38/80 | 57.9% (5.6%) |  |
| >=65 | 71/125 | 47.9% (4.7%) |  |
| Gender |  |  |  | 0.07 |
| Female | 55/119 | 55.8% (4.9%) |  |
| Male | 151/259 | 47.8% (3.2%) |  |
| Race/Ethnicity |  |  |  | **0.03** |
| White | 167/283 | 45.5% (3.0%) |  |
| Black | 9/21 | 71.1% (10.0%) |  |
| Hispanic | 27/63 | 61.3% (6.6%) |  |
| Other | 3/11 | 72.7% (13.4%) |  |
| Clinical T Stage |  |  |  | **<0.001** |
| T1 | 44/115 | 67.2% (4.5%) |  |
| T2 | 47/94 | 55.1% (5.3%) |  |
| T3 | 111/165 | 36.7% (3.9%) |  |
| T4 | 4/4 | 0.0% (.%) |  |
| Clinical M Stage |  |  |  | **<0.001** |
| No | 125/292 | 63.5% (2.9%) |  |
| Yes | 81/86 | 6.0% (2.6%) |  |
| Tumor Grade |  |  |  | **<0.001** |
| 1 | 0/3 | 100.0% (0.0%) |  |
| 2 | 41/104 | 70.1% (4.7%) |  |
| 3 | 109/196 | 48.6% (3.7%) |  |
| 4 | 56/74 | 25.8% (5.2%) |  |
| Tumor Size\* |  |  |  | **<0.001** |
| 5-<10 cm | 94/183 | 53.1% (3.8%) |  |
| <5 cm | 21/74 | 75.6% (5.2%) |  |
| >=10 cm | 91/121 | 30.7% (4.3%) |  |
| LVI |  |  |  | **<0.001** |
| No | 179/346 | 53.4% (2.8%) |  |
| Yes | 27/32 | 18.8% (6.9%) |  |
| Necrosis |  |  |  | **<0.001** |
| No | 106/221 | 58.1% (3.4%) |  |
| Yes | 99/156 | 39.5% (4.1%) |  |
| Cystic Areas |  |  |  | 0.25 |
| No | 173/311 | 48.6% (2.9%) |  |
| Yes | 32/66 | 58.6% (6.1%) |  |
| HAF Mean\* |  |  |  | **0.01** |
| <0.14 | 141/228 | 43.8% (3.4%) |  |
| >=0.14 | 62/145 | 61.0% (4.2%) |  |
| HIF-2α Mean\* |  |  |  | **<0.001** |
|  | <0.102 | 75/116 | 40.4% (4.7%) |  |
|  | 0.102-<0.307 | 66/119 | 45.4% (4.8%) |  |
|  | >=0.307 | 49/119 | 66.6% (4.4%) |  |
| HIF-1α (total) Mean\* |  |  |  | 0.08 |
| <0.0171 | 66/123 | 53.8% (4.6%) |  |
| 0.0171-<0.041 | 66/122 | 50.2% (4.7%) |  |
| >=0.041 | 67/123 | 46.0% (4.6%) |  |
| HIF-1α (Stroma) Mean\* |  |  |  | 0.13 |
| <0.005 | 61/115 | 52.3% (4.8%) |  |
| 0.005-<0.014 | 72/135 | 49.9% (4.5%) |  |
| >=0.014 | 67/119 | 47.4% (4.7%) |  |

\*These variables are continuous measures. The p-value is based on the continuous variable, and the groupings are used for presentation of time estimates only.

**Supplemental Table 5**. RPA Cut-offs Identified for Overall Survival

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Marker and within patient measure** | **Univariate Marker Split** | **Multivariate Variables Selected** | **Multivariate Marker Split** | **Best model within marker** |
| HAF |  |  |  |  |
| Min | **0.13**  **P=0.00**  HR=0.63/1.21  N=115/260 | Mets, ECOG, Tstage | NA |  |
| Median | **0.14**  **P=0.00**  HR=0.61/1.63  N=141/234 | Mets, ECOG, Tstage | NA |  |
| Max | No split found | Mets, ECOG, Tstage | NA |  |
| Mean | **0.14**  **P=0.02**  HR=0.59/1.71  N=146/229 | Mets, ECOG, Tstage | NA | X Consistently the most extreme HR and matching cut at 0.14 |
| SE | No split found | Mets, ECOG, Tstage | NA |  |
| HIF-1α |  |  |  |  |
| Min | No split found | Mets, ECOG, Tstage | NA |  |
| Median | No split found | Mets, ECOG, Tstage | NA |  |
| Max | No split found | Mets, ECOG, Tstage,**HIF1a** | **0.06**  **P=0.01** | Not matched in PFS |
| Mean | No split found | Mets, ECOG, Tstage | NA |  |
| SE | **0.03**  **p=0.01**  HR=0.48/2.07  N=274/43 | Mets, ECOG, Tstage | NA | Not matched in PFS |
| HIF-1α-Stroma |  |  |  |  |
| Min | **0.03**  **P=0.04**  HR=0.45/2.23  350/21 | Mets, ECOG, Tstage, **HIF-1α-Stroma** | **0.005**  **P=0.03** | Not matched in PFS |
| Median | **0.04**  **P=0.01**  HR=0.43/2.31  N=343/28 | Mets, ECOG, Tstage | NA |  |
| Max | **0.07**  **P=0.05**  HR=0.49/2.02  340/31 | Mets, ECOG, Tstage, **HIF-1α-Stroma** | **0.01**  **P=0.04** | Not matched in PFS |
| Mean | **0.04**  **P=0.03**  0.47/2.11  N=342/29 | Mets, ECOG, Tstage | NA |  |
| SE | **0.01**  **P=<0.005**  HR=0.50/2.00  N=258/61 | Mets, ECOG, Tstage | NA | X-Univariate match in PFS |
| HIF-2α |  |  |  |  |
| Min | **0.20**  **P=0.02**  HR=0.52/1.73  N=130/226 | Mets, ECOG, Tstage, Necrosis | NA |  |
| Median | **0.28**  **P=0.00**  HR=0.51/1.96  N=118/238 | Mets, ECOG, Tstage, Necrosis, **HIF2a** | **0.1**  **P=0.03** | X – all measures univariate significant for PFS, but only SE multivariate (cut off 0.33 univariate) |
| Max | **0.39**  **P=0.00**  HR=0.51/1.94  N=116/240 | Mets, ECOG, Tstage, Necrosis | NA |  |
| Mean | **0.33**  **P=0.00**  HR=0.60/1.24  N=104/252 | Mets, ECOG, Tstage, Necrosis | NA |  |
| SE | No split found | Mets, ECOG, Tstage, | NA | X – split found for PFS (0.09 and 0.05) |

**Supplemental Table 6**. RPA Cut-offs Identified for Progression-Free Survival

|  |  |  |  |
| --- | --- | --- | --- |
| **Marker and within patient measure** | **Univariate Marker Split** | **Multivariate Variables Selected** | **Multivariate Marker Split** |
| HAF |  |  |  |
| Min | **0.00**  **P=0.00**  HR=0.46/2.20  N=330/43 | Mets, Tstage, ECOG, Side, Race | NA |
| Median | **0.13**  **P=0.02**  HR=0.59/1.68  N=153/220 | Mets, Tstage, ECOG, Side, Race | NA |
| Max | **0.16**  **P=0.02**  HR=0.61/1.65  N=172/201 | Mets, Tstage, ECOG, Side, Race | NA |
| Mean | **0.14**  **P=0.01**  HR=0.56/1.78  N=147/226 | Mets, Tstage, ECOG, Side, Race | NA |
| SE | No split found | Mets, Tstage | NA |
| HIF-1α |  |  |  |
| Min | No split found | Mets, Tstage, ECOG, Necrosis, Race | NA |
| Median | No split found | Mets, Tstage, ECOG, Necrosis, Race | NA |
| Max | No split found | Mets, Tstage, ECOG, Necrosis, Race | NA |
| Mean | No split found | Mets, Tstage, ECOG, Necrosis, Race | NA |
| SE | No split found | Mets, Tstage, **HIF1a** | **0.004**  **P=0.03** |
| HIF-1α-Stroma |  |  |  |
| Min | No split found | Mets, Tstage, ECOG, Necrosis, Race | NA |
| Median | No split found | Mets, Tstage, ECOG, Necrosis, Race | NA |
| Max | No split found | Mets, Tstage, ECOG, Necrosis, Race | NA |
| Mean | No split found | Mets, Tstage, ECOG, Necrosis, Race | NA |
| SE | **0.01**  **P=0.02**  HR=0.54/1.84  N=261/56 | Mets, Tstage | NA |
| HIF-2α |  |  |  |
| Min | **0.28**  **P=0.00**  HR=0.48/2.08  N=96/258 | Mets, Tstage, ECOG, Side, Race | NA |
| Median | **0.23**  **P=0.00**  HR=0.48/2.06  N=154/200 | Mets, Tstage, ECOG, Side, Race | NA |
| Max | **0.37**  **P=0.00**  HR=0.41/2.41  N=121/233 | Mets, Tstage, ECOG, Side, Race | NA |
| Mean | **0.23**  **P=0.00**  HR=0.48/2.09  N=160/194 | Mets, Tstage, ECOG, Side, Race | NA |
| SE | **0.09**  **P=0.00**  HR=0.36/2.81  N=50/246 | Mets, Tstage, **HIF2a**, ECOG, Race | **0.05**  **P=0.05** |

**Supplemental Table 7**: Multivariate Progression-Free Survival by Patient Characteristics. NI = Not included

|  | | | **Model with HAF, HIF1a, and HIF2a** | | **Model with HIF1a** | | **Model without HIF1a** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **HR (95% CI)** | **P-Value** | **HR (95% CI)** | **P-Value** | **HR (95% CI)** | **P-Value** |
| **Progression-Free Survival Events/N=178/350** | | | | | **Events/N=178/350** | | **Events/N=178/350** | |
|  | Age | Unit=1 Year | 1.0 (1.0, 1.0) | 0.62 | 1.0 (1.0, 1.0) | 0.23 | 1.0 (1.0, 1.0) | 0.24 |
|  | Gender | Female vs. Male | 0.8 (0.6, 1.2) | 0.34 | 0.9 (0.7, 1.3) | 0.71 | 0.9 (0.7, 1.3) | 0.72 |
|  | Race/Ethnicity |  |  | **0.05** |  | 0.06 |  | 0.07 |
|  |  | Black vs. White | 0.9 (0.5, 1.9) |  | 1.0 (0.5, 2.0) |  | 0.9 (0.5, 1.9) |  |
|  | Hispanic vs. White | 0.9 (0.6, 1.3) |  | 0.8 (0.5, 1.3) |  | 0.8 (0.5, 1.2) |  |
|  | Other vs. White | 0.1 (0.0, 0.6) |  | 0.1 (0.0, 0.6) |  | 0.2 (0.0, 0.6) |  |
|  | ECOG | ≥1 vs. 0 | 1.6 (1.2, 2.3) | **0.003** | 1.5 (1.1, 2.0) | **0.02** | 1.4 (1.1, 2.0) | **0.02** |
|  | T Stage |  |  | **0.001** |  | **<0.001** |  | **<0.001** |
|  |  | T2 vs. T1 | 1.0 (0.6, 1.8) |  | 1.2 (0.8, 2.0) |  | 1.2 (0.8, 2.0) |  |
|  | T3 vs. T1 | 2.0 (1.2, 3.4) |  | 2.2 (1.5, 3.5) |  | 2.2 (1.4, 3.4) |  |
|  | T4 vs. T1 | 3.0 (0.6, 14.0) |  | 0.9 (0.3, 2.8) |  | 1.0 (0.3, 2.9) |  |
|  | Nodal Status | N1 vs. N0,Nx | 0.2 (0.0, 1.9) | 0.18 | 0.2 (0.0, 1.9) | 0.17 | 0.3 (0.0, 2.3) | 0.26 |
|  | M Stage | M1 vs. M0 | 6.6 (4.4, 9.9) | **<0.001** | 5.8 (4.0, 8.4) | **<0.001** | 5.7 (3.9, 8.2) | **<0.001** |
|  | Tumor Size | ≥5 vs. <5 | 1.6 (0.9, 3.0) | 0.10 | 1.5 (0.9, 2.6) | 0.12 | 1.5 (0.9, 2.5) | 0.13 |
|  | Tumor Grade |  |  | 0.39 |  | 0.24 |  | 0.18 |
|  |  | 3 vs. 1/2 | 1.3 (0.9, 2.0) |  | 1.2 (0.8, 1.8) |  | 1.3 (0.9, 1.9) |  |
|  |  | 4 vs. 1/2 | 1.3 (0.8, 2.2) |  | 1.5 (0.9, 2.4) |  | 1.6 (1.0, 2.5) |  |
|  | LVI | Yes vs. No | 1.3 (0.8, 2.1) | 0.23 | 1.5 (1.0, 2.4) | 0.06 | 1.6 (1.0, 2.4) | 0.05 |
|  | Necrosis | Yes vs. No | 1.0 (0.7, 1.4) | 0.96 | 0.9 (0.7, 1.3) | 0.59 | 0.9 (0.7, 1.3) | 0.72 |
|  | HIF1α | Unit=1 | 1.2 (0.8, 1.7) | 0.38 | 1.2 (0.9, 167) | 0.22 |  |  |
|  | HIF2α | Unit=1 | 0.9 (0.9, 1.0) | 0.22 |  |  |  |  |
|  | HAF | Unit=1 | 1.0 (0.9, 1.2) | 0.74 |  |  |  |  |