Supplementary Table 1. MiRNAs expression in cytology samples by Bethesda categories in all series.

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| **miRNAs in cytology** |  | | **By Bethesda categories** | | |
| n | cytology | median | P25 - P75 | min - max value |
| miRNA146 | 96  03  20  47  26 | ND  Benign  AUS + FN  SM+ M | 0.005  0.161  0.756  1.275 | 0.000 - 0.000  0.071 – 1.339  0.079 – 7.395  0.004 – 138.81 | 0.000 –0.21  0.000 – 853.8  0.000 – 1768,34  0.000 – 1627.93 |
| miRNA221 | 97  03  20  48  26 | ND  Benign  AUS + FN  SM+ M | 0.062  0.237  0.169  0.400 | 0.000 – 0.000  0.062 – 1.802  0.043 – 1.095  0.000 – 8.265 | 0.000 –0.081  0.000 – 11.033  0.000 – 51.976  0.000 – 24.626 |
| miRNA222 | 91  03  18  44  26 | ND  Benign  AUS + FN  SM+ M | 0.903  1.951  1.045  7.581 | 0.000 –0.000  0.830 –5.545  0.343 – 14.592  .004 – 121.022 | 0.000 –1.501  0.000 – 1120.686  0.000 – 2604.770  0.000 – 1111.663 |
| miRNA15a | 98  03  21  48  26 | ND  Benign  AUS + FN  SM+ M | 0.412  0.745  1.198  0.691 | 0.000 –0.000  0.408 – 1.148  0.475 – 4.772  0.000 – 2.629 | 0.000 – 0.772  0.000 – 7.390  0.000 – 47.341  0.000 – 7.831 |

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| **MiRNAs expression in cytology** |  | | **Histology diagnosis** | | | |
| n | Final Diagnosis | Median\* | P25 - P75 | min - max value | p-value\*\* |
| miRNA146 | 96  11  85 | Benign  Malignant | 0.308  0.489 | 0.141 - 1.530  0.045 - 16.80 | 0.086 - 4.394  0.000 - 1768.34 | 0.895 |
| miRNA221 | 97  11  86 | Benign  Malignant | 0.535  0.172 | 0.155 - 2.351  0.039 - 2.636 | 0.035 - 5.242  0.000 - 51.976 | 0.169 |
| miRNA222 | 97  11  86 | Benign  Malignant | 0.914  1.460 | 0.506 - 2.493  0.330 - 32.199 | 0.089 - 6.358  0.000 - 2604,77 | 0.402 |
| miRNA15a | 98  11  87 | Benign  Malignant | 1.053  0.686 | 0.745 – 4.349  0.415 – 2.999 | 0.016 - 7.390  0.000 - 47.341 | 0.402 |

Supplementary Table 2. MiRNAs expression in cytology samples by histology diagnosis in all series.Supplementary Table 3. Five highest extreme frequencies of miRNAs expression in cytology samples by histology diagnosis in all series.

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| --- | --- | --- | --- | --- | --- |
| **Histology diagnosis** | **Highest values**  **of miRNAs expression in cytology** | | | |  |
| miRNA-146 | miRNA-221 | miRNA-222 | miRNA-15a |
| Benign | 4.394  2.881  1.529  0.770  0.610 | 5.242  3.978  2.351  1.401  0.677 | 6.358  3.139  1.846  1.384  0.914 | 7.390  5.620  4.349  1.242  1.193 |
| Malignant | 1768.341  1627.930  1121.931  1041.914  958.423 | 51.976  48.630  24.626  16.130  11.653 | 2604.770  1120.686  1112.533  1111.663  1106.747 | 47.341  11.342  10.989  9.556  9.486 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **miRNAs in histology**  n=106 |  | | **Histological subtypes** | | | | |
| Benign  n=13 | WDT-UMP  n=2 | | NIFT  n=4 | PTC  n=81 | FTC  n=4 | HCC  n=2 |
| **miRNA-146**  n= 60  Median  P25-P75  Min – Max | n=8  0.66  0.392 – 2.456  0.322 – 5.341 | n=1  -  -  - | | n=2  0.226  0.142 – 0.  0.142 – 0.310 | n=46  65.667  8.351 – 1316.098  0.016 –27755.752 | n=2  0.227­ – 0.  0.025 – 0.  0.025 – 0.428 | n=1  -  -  - |
| **miRNA-221**  n= 76  Median  P25-P75  Min – Max | n=10  1.312  0.781 – 1.798  0.192 – 4.395 | n=1  -  -  - | | n=4  1.918  0.385 – 4.092  0.012 – 4.678 | n=57  5.45  1.582 –10.900  0.368 – 63.304 | n=2  0.115  0.108 – 0.  0.108 – 0.124 | n=2  6.278  3.297 – 0.  3.297 – 9.260 |
| **miRNA-222**  n= 78  Median  P25-P75  Min – Max | n=10  1.067  0.645 – 2.544  0.328 – 4.348 | n=1  -  -  - | | n=4  2.465  0.626 – 9.693  0.271 – 11.843 | n=59  3.511  1.183 – 13.315  0.115 – 3006.7 | n=2  0.134  0.124 – 0.  0.124 – 0.143 | n=2  16.21  7.7 – 0.  7.7 – 0. 24.72 |
| **miRNA-15a**  n= 77  Median  P25-P75  Min – Max | n=10  0.683  0.510 – 1.610  0.282 – 2.514 | n=1  -  -  - | | n=4  1.020  0.835 – 2.177  0.779 – 2.556 | n=58  2.682  1.396 – 37.388  0.479 – 99.641 | n=2  1.594  1.439 – 0.  1.439 – 1.747 | n=2  0.236  0.231 – 0.  0.231 – 0.241 |

Supplementary Table 4. MiRNAs expression in histology within histological subtypes in all series.

Legend: WDT-UMP: Well differentiated thyroid tumor of uncertain malignant potential; NIFT: noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; HCC: Hürthle cell carcinoma: not available data to estimate summary measures.

Supplementary Table 5. Association of the miRNAs expression levels and the presence of genetic mutations in cytology samples in PTCs.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | | | | | | | | |
| **miRNAs in cytology** | | | | | | | |
| **Genetic**  **mutations in cytology** |
| miRNA-146 | | miRNA-221 | | miRNA-222 | | miRNA-15a | | | |
| n | Median | n | Median | n | Median | n | Median | | |
| *TERTp*  Absent  Present  p-value | 84  74  10 | 0.619  0.880  0.730 | 85  75  10 | 0.247  0.170  0.754 | 80  70  10 | 1.460  0.963  0.391 | 86  76  10 | 0.765  2.044  0.609 | | |
| *BRAF*  Absent  Present  p-value | 84  62  22 | 0.619  0.905  0.555 | 85  63  22 | 0.198  0.341  0.779 | 80  58  22 | 1.133  3.709  0.338 | 86  64  22 | 1.123  0.589  0.135 | | |
| *RAS*  Absent  Present  p-value | 83  64  19 | 0.696  0.219  0.193 | 84  65  19 | 0.266  0.191  0.096 | 79  61  18 | 1.420  1.010  0.082 | 86  66  19 | 0.801  1.204  0.792 | | |

Legend: *TERTp*: telomerase reverse transcriptase promoter; *BRAF*: B-Raf proto-oncogene, serine/threonine kinase; *NRAS*: NRAS proto-oncogene, GTPase; *HRAS*: HRas proto-oncogene, GTPase, and *KRAS*—*KRAS* proto-oncogene, GTPase.

Supplementary Table 6. A. Associations between miR-146b expressionand clinicopathological features in Papillary Thyroid Carcinomas.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| miR-146b and  clinicopathological characteristics n =54 (100%) | Median | P25 - P75 | Min - Max value | p-value |
| Mean tumor size (SD) (mm)  (n=54) | - | - | - | 0.179 |
| Extra thyroidal invasion  Absent 42 (77.8)  Present 12 (22.2) | 27.227  147.041 | 3.127 - 389.557  3.333 - 1402.208 | 0.016 - 6476.520  0.473 - 27755.768 | 0.318 |
| Capsule invasion  Absent 29 (53.7)  Present 25 (46.3) | 8.733  126.683 | 1.131 - 119.808  20.400 - 1377.380 | 0.016 - 5276,991  0.473 - 27755,768 | **0.011** |
| Vascular invasion  Absent 45 (83.3)  Present 9 (16.7) | 27.945  95.902 | 3.119 - 448.500  13.774 - 2771.874 | 0.016 - 6476.520  0.473 - 27755.768 | 0.270 |
| Lymphatic invasion  Absent 48 (88.9)  Present 6 (11.1) | 29.856  732.253 | 3.215 - 532.402  1.215 - 10022.989 | 0.016 – 6476.520  0.473 – 27755.768 | 0.475 |
| Psammoma bodies  Absent 47 (87)  Present 7 (13) | 22.303  160.507 | 3.006 - 616.304  61.201 - 5276.991 | 0.016 – 6476.520  32.819 - 27755.768 | **0.019** |
| Calcifications  Absent 43 (79.6)  Present 11 (20.4) | 22.303  160.507 | 2.725 - 280.695  32.819 - 5276.991 | 0.016 - 5268.565  7.207 - 27755.768 | **0.010** |
| Lymph node metastases  Absent 49 (90.7)  Present 05 (9.3) | 32.819  3.070 | 3.740 – 843.629  0.968 – 746.444 | 0.016 – 27755.768  0.473 – 1431.686 | 0. 350 |

Supplementary Table 6. B. Associations between miR-221 expressionand clinicopathological features in Papillary Thyroid Carcinomas.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| miR-221 and  clinicopathological characteristics n =67 (100%) | Median | P25 - P75 | Min - Max value | p-value |
| Mean tumor size (SD) (mm)  n =67 | - | - | - | 0.817 |
| Extra thyroidal invasion  Absent 54 (80.6)  Present 13 (19.4) | 2.727  7.786 | 1.034 - 9.257  2.223 - 14.415 | 0.192 - 36.928  1.545 - 63.304 | 0.078 |
| Capsule invasion  Absent 39 (58.2)  Present 28 (41.8) | 1,618  8.064 | 0.878 - 6.802  2.855 - 15.441 | 0.192 - 18.908  0.368 - 63.304 | **<0.001** |
| Vascular invasion  Absent 56 (83.6)  Present 11 (16.4) | 2.355  12.518 | 1.068 - 8,065  5.452 - 23,279 | 0.192 - 34.725  2.342 - 2.342 | **<0.001** |
| Lymphatic invasion  Absent 60 (89.6)  Present 7 (10.4) | 2.900  16.415 | 1.240 - 1240  1.820 - 23.279 | 0.192 - 36.928  0.368 - 63.304 | 0.078 |
| Oncocytic component  Absent 58 (86.6)  Present 9 (13.4) | 2.342  12.414 | 1.070 - 7.972  8,283 - 28.598 | 3.006 - 616.304  5.452 - 63.304 | **0.002** |
| Calcifications  Absent 54 (80.6)  Present 13 (19.4) | 2.403  8.224 | 1.072 - 8.126  3.376 - 16.974 | 0.192 - 63.304  0.368 - 23.279 | **0.031** |
| Lymph node metastases  Absent 61 (91)  Present 06 (9) | 3.190  5.413 | 1.145 - 10.018  1,751 - 11.378 | 0.192 - 63.304  1.545 - 17.532 | 0.499 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| miR-222 and  clinicopathological characteristics n =69 (100%) | Median | P25 - P75 | Min - Max value | p-value |
| Mean tumor size (SD) (mm) (n=69) | - | - | - | 0.253 |
| Extra thyroidal invasion  Absent 56 (81.2)  Present 13 (18.8) | 2.210  14.006 | 0.870 - 5.603  4.238 - 36.416 | 0.114 - 43,231  0.908 - 3006.772 | **<0.001** |
| Capsule invasion  Absent 39 (56.5)  Present 30 (43.5) | 1.669  5.284 | 0.717 - 4.347  2.014 - 14.113 | 0.114 - 68.403  0.861 - 3006.772 | **0.005** |
| Vascular invasion  Absent 57 (82.6)  Present 12 (17.4) | 2.222  10.575 | 0.879 - 4.806  7.220 - 38.986 | 0.114 - 68,403  1.392 - 3006.772 | **<0.001** |
| Lymphatic invasion  Absent 61 (88.4)  Present 8 (11.6) | 2.325  8.172 | 0.902 - 8.224  3.840 - 36.370 | 0.114 - 68.403  1.392 - 3006.772 | **0.020** |
| Psammoma bodies  Absent 58 (84)  Present 11 (16) | 2.251  8.230 | 0. 888 - 7.806  3.465 - 15.210 | 0.114 - 68.403  1,392 - 3006.772 | **0. 010** |
| Calcifications  Absent 55 (79.7)  Present 14 (20.3) | 2.222  7.949 | 0.861 - 5.921  3.102 - 19.672 | 0. 114 - 68,403  1.392 - 3006.772 | **0.006** |
| Oncocytic component  Absent 50 (72.5)  Present 19 (27.5) | 1.775 13.211 | 0.843 - 6.496  3.673 - 32.168 | 0.114 - 3006.,772  2,222 - 41.556 | **0.008** |
| Inflammatory infiltrate  Absent 50 (72.5)  Present 19 (27.5) | 2.040  4.965 | 0.888 - 7.806  3.354 - 16.633 | 0.114 - 68.403  0.429 - 3006.772 | **0.019** |
| Tall cells  Absent 59 (85.5)  Present 10 (14.5) | 2.222  8.230 | 0.897 - 8.219  4.055 - 36.352 | 0.114 - 68,403  3.354 - 3006.772 | **0.017** |
| Focality  Unifocal 40 (58)  Multifocal 29 (42) | 3.200  7.070 | 1.000 - 7.669  1.475 - 27.044 | 0.114 - 68.403  0.196 - 3006.772 | **0. 049** |
| Lymph node metastases  Absent 62 (89.9)  Present 07 (10.1) | 3.093  4.965 | 0. 951 - 12.659  1.392 - 8.675 | 0. 114 - 3006.772  0. 908 - 41.556 | 0. 330 |

Supplementary Table 6.C. Associations between miR-222 expressionand clinicopathological features in Papillary Thyroid Carcinomas.

Supplementary Table 6. D. Associations between miR-15a expressionand clinicopathological features in Papillary Thyroid Carcinomas.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| miR-15a and  clinicopathological characteristics n =68 (100%) | Median | P25 - P75 | Min - Max value | p-value |
| Mean tumor size (SD) (mm) (n=68) | - | - | - | 0.649 |
| Extra thyroidal invasion  Absent 56 (82.4)  Present 12 (17.6) | 2.210  1.333 | 1.309 - 37.281  1.194 - 3.570 | 0.282 - 99.640  0.847- 52.086 | 0.182 |
| Capsule invasion  Absent 39 (57.4)  Present 29 (42.6) | 1.577  19.882 | 0.881 - 4.089  1.527- 41.928 | 0.282 - 81,366  0.712 - 99.640 | **0.006** |
| Focality  Unifocal 39 (57.4)  Multifocal 29 (42.6) | 1.867  2.561 | 1.249 - 37.278  1.745 - 38.385 | 0.473 - 99.640  0.712 - 55.047 | **0. 041** |
| Lymph node metastases  Absent 61 (89.7)  Present 07 (10.3) | 2.475  1.374 | 1.263 - 37.257  0.935 - 19.882 | 0. 282 - 99.640  0. 847 - 37.705 | 0. 380 |