**Title:** Automated digital TIL analysis (ADTA) adds prognostic value to standard assessment of depth and ulceration in primary melanoma

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**Supplemental Table 1.** Univariable Cox regression analysis of disease-specific survival on Training cohort, including pathology TIL grade, depth, ulceration, and sentinel lymph node biopsy (SLNB) status.

Univariable cox analysis using training cohort.

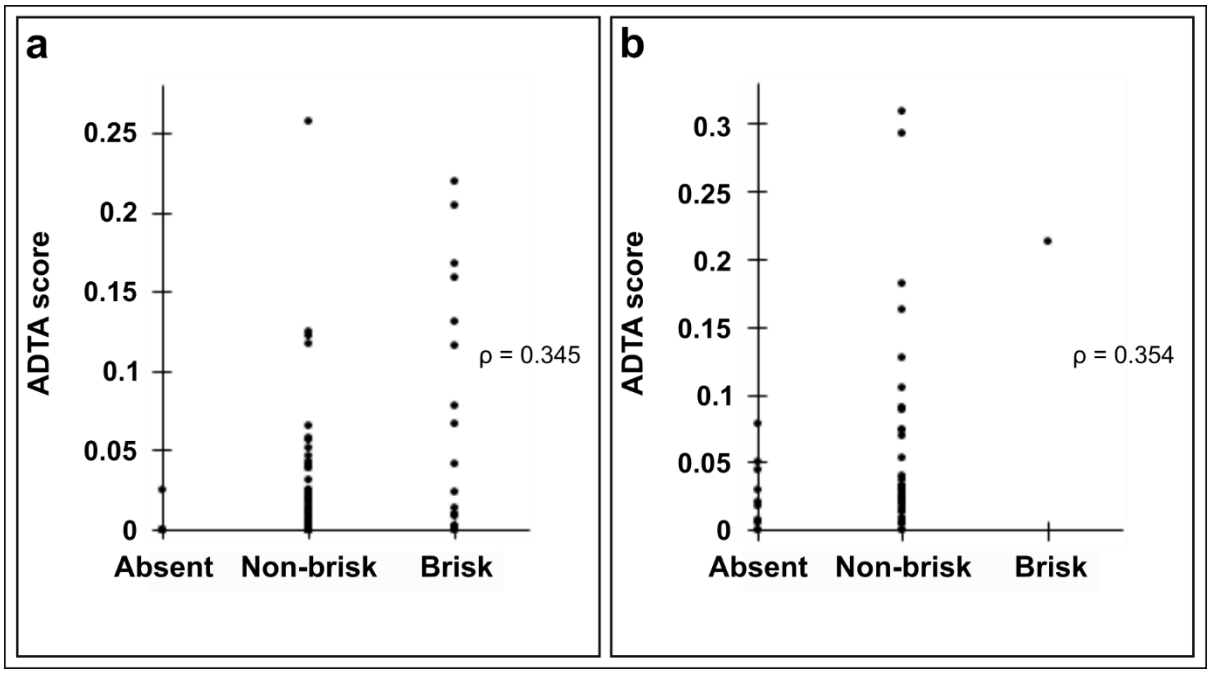
| | Hazard ratio | 95% CI | *P* |
|---|---|---|---|
| **Pathology TIL grade*** | 0.35 | 0.00-0.95 | 0.039 |
| **Depth** | 1.32 | 0.78-2.25 | 0.306 |
| **Ulceration** | 2.47 | 0.91-6.73 | 0.076 |
| **SLNB*** | 2.98 | 1.04-8.55 | 0.043 |

**Supplemental Table 2**. Validation demographics, separated by institution**.**

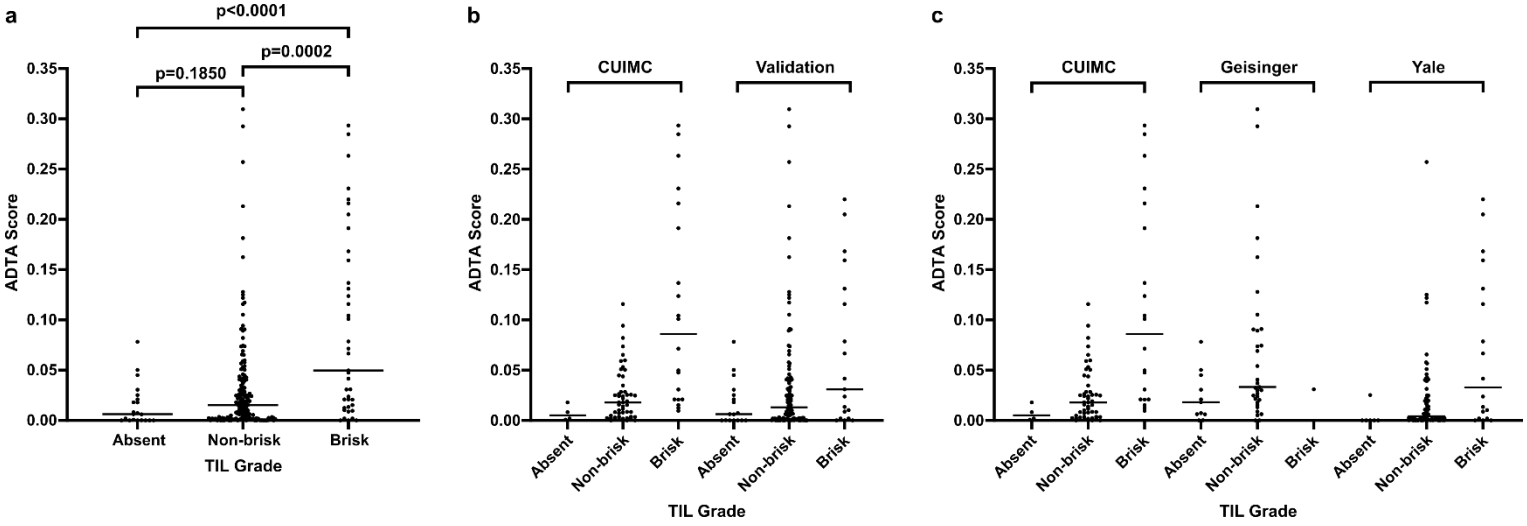
| | Yale | Geisinger |
|---|---|---|
| **Clinical characteristics** | **(n = 100)** | **(n = 45)** |
| Sex, *n* (%) | | |
| Male | 48 (48.0) | 24 (53.3) |
| Female | 52 (52.0) | 21 (46.7) |
| Age | | |
| Median, *n* (range) | 61 (25-84) | 65 (20-90) |
| Location of tumor, *n* (%) | | |
| Trunk | N/A | 29 (64.4) |
| Extremity | N/A | 16 (35.6) |
| **Pathologic characteristics** | | |
| Depth (mm) | | |
| Median, *n* (range) | 2.3 (0.2-8.3) | 3.5 (0.7-13.0) |
| Ulceration, *n* (%) | | |
| Absent | 61 (61.0) | 25 (55.6) |
| Present | 39 (39.0) | 20 (44.4) |
| Unknown | 0 (0.0) | 0 (0.0) |
| TILs | | |
| Absent | 6 (6.0) | 11 (24.5) |
| Non-brisk | 76 (76.0) | 32 (71.1) |
| Brisk | 18 (18.0) | 1 (2.2) |
| Unknown | 0 (0.0) | 1 (2.2) |
| Microsatellite lesions, *n* (%) | | |
| Absent | 75 (75.0) | 39 (86.7) |
| Present | 25 (25.0) | 6 (13.3) |
| Unknown | 0 (0.0) | 0 (0.0) |
| **Staging Characteristics** | | |
| T-stage, *n* (%) | | |
| T1a or T1b | 22 (22.0) | 1 (2.2) |
| T2a | 14 (14.0) | 0 (0.0) |
| T2b or T3a | 28 (28.0) | 16 (35.6) |
| T3b or T4a | 22 (22.0) | 18 (40.0) |
| T4b | 14 (14.0) | 10 (22.2) |
| Unknown | 0 (0.0) | 0 (0.0) |
| SLNB status, *n* (%) | | |
| Completed | 0 (0.0) | 40 (88.9) |
| Positive, *n* (% of completed) | 0 (0.0) | 20 (50.0) |
| Negative, *n* (% of completed) | 0 (0.0) | 20 (50.0) |
| Not completed | 0 (0.0) | 5 (11.1) |
| Unknown | 100 (100.0) | 0 (0.0) |
| Stage, *n*(%) | | |
| I | 30 (30.0) | 1 (2.2) |
| II | 45 (45.0) | 21 (46.7) |
| III | 25 (25.0) | 23 (51.1) |
| **Outcome characteristics** | | |
| Patient follow-up (months) | | |
| Median, *n* (range) | 68.7 (1.4-456.2) | 76.0 (9-142) |
| DMR, *n* (%) | | |
| Distant recurrence | 44 (44.0) | 25 (55.6) |
| No distant recurrence or local recurrence only | 56 (56.0) | 20 (44.4) |
| OS, *n* (%) | | |
| Alive (at least 2 years) | 26 (26.0) | 22 (48.9) |
| Dead | 74 (74.0) | 23 (51.1) |
| DSS, *n* (%) | | |
| Alive or NED at death | 56 (56.0) | 26 (57.8) |
| Median follow-up (months) | 114.4 | 94.0 |
| Dead with melanoma | 44 (44.0) | 19 (42.2) |
| Median follow-up (months) | 39.0 | 28.0 |
| Unknown | 0 (0.0) | 0 (0.0) |

Abbreviations: DMR, distant metastatic recurrence; DSS, disease-specific survival; NED, no evidence of disease; OS, overall survival

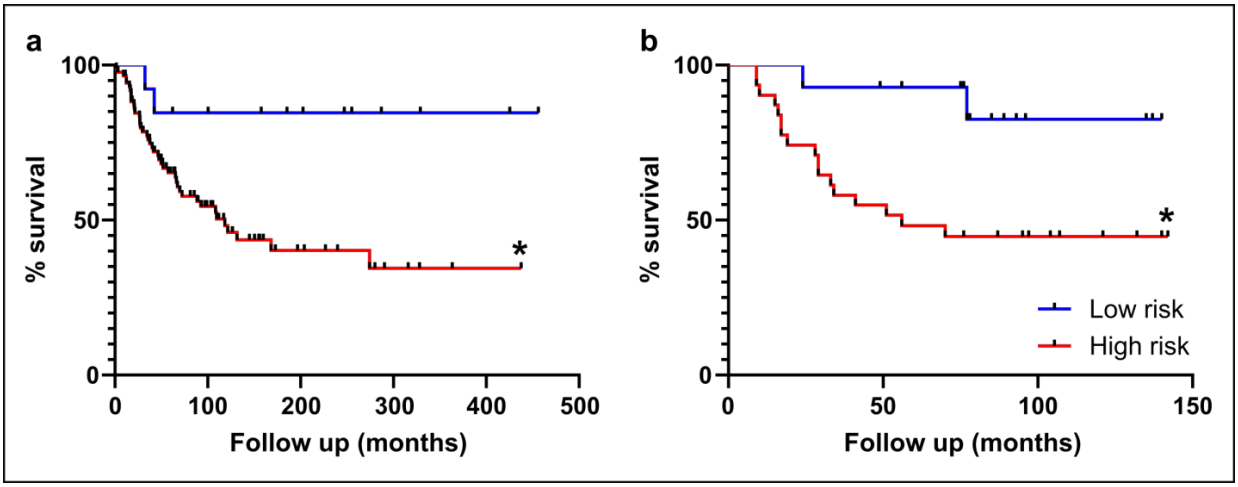
**Supplemental Figure 1. ADTA correlated with pathologist TIL grading.** Correlation between ADTA score and pathologist TIL grading defined as absent, non-brisk, or brisk for (a) Yale cohort (ρ=0.345, p<0.001 using Spearman's rank correlation coefficient) and (b) Geisinger cohort (ρ=0.354, p=0.019 using Spearman's rank correlation coefficient).



**Supplementary Figure 2. ADTA score distributed by pathologist TIL grade.** (a) Analysis of variance between ADTA scores of all patients stratified by their corresponding patient TIL grade (Kruskal-Wallis, p<0.0001; Dunn multiple comparison p values of 0.1850 for Absent vs. Non-brisk, <0.0001 for Absent vs. Brisk, and 0.0002 for Non-brisk vs. Brisk). (b) Distribution of ADTA scores by TIL grade within the training (CUIMC) and validation (GHS and YMS) cohorts. (c) Distribution of ADTA scores by TIL grade within each institution.



**Supplemental Figure 3. ADTA performance on Yale and Geisinger populations, individually.** KM curves for disease-specific survival on (a) Yale population (p=0.0139 using log rank (Mantel-Cox) test) and (b) Geisinger population (p=0.0141 using log rank (Mantel-Cox) test).



**Supplemental Table 3.** Univariable Cox regression analysis of disease-specific survival on Yale and Geisinger cohorts, including ADTA, depth, ulceration, T-stage, pathology TIL grade, and SLNB status.

Univariable cox analysis using validation cohort.

| | Yale | | Geisinger | |
|---|---|---|---|---|
| | **Hazard ratio (95% CI)** | ***P*** | **Hazard ratio (95% CI)** | ***P*** |
| **ADTA** | 5.01 (1.21-20.80) | 0.027 | 5.17 (1.19-22.41) | 0.028 |
| **Depth** | 1.59 (1.17-2.16) | 0.003 | 1.54 (0.76-3.11) | 0.231 |
| **Ulceration** | 1.34 (0.74-2.44) | 0.333 | 2.86 (1.03-7.96) | 0.044 |
| **T-Stage** | 1.22 (1.07-1.40) | 0.004 | 1.36 (0.97-1.90) | 0.071 |
| **Pathology TIL grade** | 0.50 (0.00-0.95) | 0.035 | 0.78 (0.31-1.98) | 0.598 |
| **SLNB** | N/A | N/A | 1.51 (0.57-3.97) | 0.406 |

**Supplemental Table 4.** Multivariable Cox regression analysis of disease-specific survival on validation cohort, including pathology TIL grade, depth, and ulceration.

Multivariable cox analysis using validation cohort.

| | **Hazard ratio** | **95% CI** | ***P*** |
|---|---|---|---|
| **Pathology TIL grade** | 0.79 | 0.46-1.38 | 0.414 |
| **Depth*** | 1.40 | 1.03-1.89 | 0.031 |
| **Ulceration** | 1.29 | 0.77-2.18 | 0.335 |

**Supplemental Table 5.** Multivariable Cox regression analysis of disease-specific survival on validation cohort, including ADTA and stage.

Multivariable cox analysis using validation cohort.

| | **Hazard ratio** | **95% CI** | ***P*** |
|---|---|---|---|
| **ADTA**** | 4.61 | 1.67-12.71 | 0.003 |
| **Stage**** | 1.77 | 1.24-2.53 | 0.002 |