**Supplementary Material**

Table S1. Consensus rate among pathologists in assessing the density of intra-tumoral TILs, and the frequency of TIL density levels estimated by each pathologist categorized in different cut-off systems.

|  |  |
| --- | --- |
| **Consensus** | **Rate (%)** |
|  System 1 |  |
|  Positive | 42 (48.84%) |
|  Negative | 4 (4.65%) |
|  Partially positive | 40 (46.51%) |
|  System 2 |  |
|  Positive | 27 (31.40%) |
|  Negative | 11 (12.79%) |
|  Partially positive | 48 (55.81%) |
|  System 3 |  |
|  Positive | 30 (34.88%) |
|  Negative | 10 (11.63%) |
|  Partially positive | 46 (53.49%) |
|  System 4 |  |
|  Positive | 48 (55.81%) |
|  Partially positive | 38 (44.19%) |
| **Cut-off systems** | **Frequency (Low; Moderate; High levels)** |
| System1 |  |
|  OBS1\* | (2; 47; 37) |
|  OBS2 | (9; 57; 20) |
|  OBS3 | (13; 57; 16) |
|  System 2 |  |
|  OBS1 | (4; 30; 52) |
|  OBS2 | (24;25;37) |
|  OBS3 | (34;19;33) |
|  System 3 |  |
|  OBS1 | (22; 23; 41) |
|  OBS2 | (37; 20; 29) |
|  OBS3 | (45; 12; 29) |
|  System 4 |  |
|  OBS1 | (Low: 45; High:41) |
|  OBS2 | (Low: 58; High:28) |
|  OBS3 | (Low: 56; High:30) |

\* OBS1: observer 1, OBS2: observer 2, OBS3: observer 3.

Table S2. Pairwise agreement assessment for intra-tumoral stromal TILs scoring

|  |  |  |  |
| --- | --- | --- | --- |
| **Cut-off systems****System 1** | **Consensus (CI\*)** | **Kappa value (P\*\*)** | **McNemar’s Test (P\*\*\*)** |
| OBS1-OBS2 # | 0.64 (CI: 0.53, 0.74) | 0.33 (<0.001) | <0.001 |
| OBS1-OBS3 | 0.57 (CI: 0.46, 0.68) | 0.22 (<0.01) | <0.001 |
| OBS2-OBS3 | 0.72 (CI: 0.61, 0.81) | 0.44 (<0.001) | 0.43 |
| **System 2** |  |
| OBS1-OBS2 | 0.48 (CI: 0.37, 0.59) | 0.16 (0.02) | <0.001 |
| OBS1-OBS3 | 0.45 (CI: 0.35, 0.57) | 0.19 (<0.01) | <0.001 |
| OBS2-OBS3 | 0.57 (CI: 0.46, 0.68) | 0.35 (<0.001) | 0.10 |
| **System 3** |  |
| OBS1-OBS2 | 0.51 (CI: 0.40, 0.62) | 0.27 (<0.001) | 0.004 |
| OBS1-OBS3 | 0.49 (CI: 0.38, 0.60) | 0.23 (<0.001) | 0.002 |
| OBS2-OBS3 | 0.58 (CI: 0.38, 0.60) | 0.33 (<0.001) | 0.24 |
| **System 4** |  |
| OBS1-OBS2 | 0.66 (CI: 0.55, 0.76) | 0.31 (<0.01) | 0.03 |
| OBS1-OBS3 | 0.71 (CI: 0.60, 0.80) | 0.41 (<0.001) | 0.05 |
| OBS2-OBS3 | 0.74 (CI: 0.64, 0.83) | 0.43 (<0.001) | 0.83 |

\* 95% confidence interval for agreement between two pathologists.

\*\*Cohen’s Kappap-value; p-value<0.05 means that there is more than zero agreement.

\*\*\* McNemar’s p-value <0.05 means that the observers disagree.

# OBS1: observer 1, OBS2: observer2, OBS3: observer 3.

Table S3. Consensus rate between pathologists for estimating the tumor front TILs, and the frequency of TIL density levels scored by each pathologist in the different cut-off systems.

|  |  |
| --- | --- |
| **Consensus** | **Rate (%)** |
|  System 1 |  |
|  Positive | 32 (37.21%) |
|  Negative | 3 (3.49%) |
|  Partially positive | 51 (59.30%) |
|  System 2 |  |
|  Positive | 33 (38.37%) |
|  Negative | 4 (4.65%) |
|  Partially positive | 48 (56.98%) |
|  System 3 |  |
|  Positive | 33 (38.37%) |
|  Negative | 11 (12.79%) |
|  Partially positive | 42 (48.84%) |
|  System 4 |  |
|  Positive | 42 (48.84%) |
|  Partially positive | 44 (51.16%) |
| **Cut-off systems** | **Frequency (Low; Moderate; High levels)** |
| System1 |  |
|  OBS1\* | (7; 29; 50) |
|  OBS2 | (9; 55; 22) |
|  OBS3 | (13; 53; 20) |
|  System 2 |  |
|  OBS1 | (7; 13; 66) |
|  OBS2 | (26; 21; 39) |
|  OBS3 | (27; 19; 40) |
|  System 3 |  |
|  OBS1 | (18; 9; 59) |
|  OBS2 | (32; 26; 28) |
|  OBS3 | (32; 22; 30) |
|  System 4 |  |
|  OBS1 | (Low: 27, High: 59) |
|  OBS2 | (Low: 58, High: 28) |
|  OBS3 | (Low: 54, High: 32) |

\* OBS1: observer 1, OBS2: observer2, OBS3: observer 3.

Table S4. Pairwise agreement evaluation for estimating stromal TILs in tumor front

|  |  |  |  |
| --- | --- | --- | --- |
| **Cut-off systems****System 1** | **Consensus (CI\*)** | **Kappa value (P\*\*)** | **McNemar’s Test (P\*\*\*)** |
| OBS1-OBS2 # | 0.54 (CI: 0.42, 0.64) | 0.27 (<0.001) | <0.001 |
| OBS1-OBS3 | 0.46 (CI: 0.35, 0.57) | 0.16 (0.02) | <0.001 |
| OBS2-OBS3 | 0.72 (CI: 0.61, 0.81) | 0.47 (<0.001) | NA |
| **System 2** |  |
| OBS1-OBS2 | 0.50 (CI: 0.39, 0.61) | 0.16 (0.02) | <0.001 |
| OBS1-OBS3 | 0.52 (CI: 0.41, 0.63) | 0.19 (0.01) | <0.001 |
| OBS2-OBS3 | 0.63 (CI: 0.52, 0.73) | 0.41 (<0.001) | 0.67  |
| **System 3** |  |
| OBS1-OBS2 | 0.51 (CI: 0.40, 0.62) | 0.27 (<0.001) | <0.001 |
| OBS1-OBS3 | 0.52 (CI: 0.41, 0.63) | 0.28 (<0.001) | <0.001 |
| OBS2-OBS3 | 0.60 (CI: 0.49, 0.71) | 0.40 (<0.001) | 0.81 |
| **System 4** |  |
| OBS1-OBS2 | 0.57 (CI: 0.46, 0.68) | 0.25 (<0.01) | <0.001 |
| OBS1-OBS3 | 0.66 (CI: 0.55, 0.76)  | 0.40 (<0.001) | <0.001 |
| OBS2-OBS3 | 0.72 (CI: 0.61, 0.81)  | 0.38 (<0.001) |  |

\* 95% confidence interval for agreement between two pathologists.

\*\*Cohen’s Kappap-value; p value<0.05 means that there is more than zero agreement.

\*\*\* McNemar’s p-value <0.05 means that the observers disagree.

# OBS1: observer 1, OBS2:observer2, OBS3: observer 3.

Table S5. Consensus rate between pathologists for estimating the TSR and frequency of TSR levels estimated by each pathologist.

|  |  |
| --- | --- |
| **Consensus** | **Rate (%)** |
|  Positive | 75 (87.21%) |
|  Partially positive | 11 (12.79%) |
| **Pathologist** | **Frequency (%)** |
|  OBS1 | Poor-stroma: 78 (90.70%), Rich-stroma: 8 (9.30%) |
|  OBS2 | Poor-stroma: 78 (90.70%), Rich-stroma: 8 (9.30%) |
|  OBS3 | Poor-stroma: 76 (88.37%), Rich-stroma: 10 (11.63%) |

# OBS1: observer 1, OBS2:observer2, OBS3: observer 3.

Table S6. Pairwise agreement evaluation between pathologists for assessing the TSR

|  |  |  |  |
| --- | --- | --- | --- |
| **Pathologists** | **Consensus (CI\*)** | **Kappa value (P\*\*)** | **McNemar’s Test (P\*\*\*)** |
| OBS1-OBS2 # | 0.95 (CI: 0.89, 0.99) | 0.72 (<0.001) | 1 |
| OBS1-OBS3 | 0.91 (CI: 0.83, 0.96) | 0.51(<0.001) | 0.72 |
| OBS2-OBS3 | 0.86 (CI: 0.77, 0.93) | 0.26 (0.02) | 0.77 |

\* 95% confidence interval for agreement between two pathologists

\*\*Cohen’s Kappap-value; p value<0.05 means that there is more than zero agreement

\*\*\* McNemar’s p-value <0.05 means that the observers disagree

# OBS1: observer 1, OBS2:observer2, OBS3: observer 3.