

Table S1. Clinicopathological characteristics of group C

| Variable | n = 49 | SARIFA-positive (n = 29) | SARIFA-negative (n = 20) | P-value |
|---------------------------------|---------------|-------------------------------------|-------------------------------------|----------------|
| Median Age (years) | 71 (61-77) | 72 (61-78) | 71 (61-77) | 0.458 |
| Median Lymph Node Harvest (n) | 38 (29-49) | 36 (28-53) | 39 (30-49) | 0.776 |
| Median Positive Lymph Nodes (n) | 0 (0-2) | 1 (0-4) | 0 (0-1) | 0.992 |
| Sex | | | | 0.842 |
| female | 20 (41%) | 12 (41%) | 8 (40%) | |
| male | 29 (59%) | 17 (59%) | 12 (60%) | |
| T status | | | | 0.042 |
| pT3 | 35 (71%) | 12 (41%) | 15 (75%) | |
| pT4 | 14 (29%) | 17 (59%) | 5 (25%) | |
| Grading | | | | 0.700 |
| low grade | 41 (84%) | 25 (86%) | 16 (80%) | |
| high grade | 8 (16%) | 4 (14%) | 4 (20%) | |
| Vascular invasion | | | | 0.234 |
| negative | 36 (73%) | 19 (66%) | 17 (85%) | |
| positive | 13 (27%) | 10 (34%) | 3 (15%) | |
| Lymphatic invasion | | | | 0.512 |
| negative | 37 (76%) | 23 (79%) | 14 (70%) | |
| positive | 12 (24%) | 6 (21%) | 6 (30%) | |
| Location | | | | 0.842 |
| right | 28 (57%) | 12 (41%) | 8 (40%) | |
| left | 21 (43%) | 17 (59%) | 12 (60%) | |
| MMS | | | | 1.000 |
| stable | 40 (95%)* | 25 (96%) | 16 (94%) | |
| unstable | 2 (5%)* | 1 (4%) | 1 (6%) | |
| Adjuvant Therapy | | | | 0.272 |
| no | 23 (47%) | 13 (45%) | 13 (65%) | |
| yes | 26 (53%) | 16 (55%) | 7 (35%) | |
| Death | | | | 0.496 |
| no | 39 (80%) | 22 (76%) | 13 (65%) | |
| yes | 10 (20%) | 7 (24%) | 3 (15%) | |

Table S2. Spearman Correlation of morphological biomarkers

| | Tumor budding | PDC | SG | Jass |
|----------------------|----------------------|------------|-----------|-------------|
| SARIFA | 0.267 | 0.281 | 0.148 | 0.217 |
| | 0.0633 | 0.0503 | 0.308 | 0.134 |
| | 49 | 49 | 49 | 49 |
| Tumor budding | 0.710 | 0.250 | 0.253 | |
| | 0.000000200 | 0.0832 | 0.0788 | |
| | 49 | 49 | 49 | |
| PDC | | 0.0671 | 0.102 | |
| | | 0.645 | 0.482 | |
| | | 49 | 49 | |

| | |
|-----------|-------|
| SG | 0.231 |
| | 0.110 |
| | 49 |

Jass

Legend: SARIFA, Stroma AReactive Invasion Front Areas; PDC, poorly differentiated clusters; SG, Stroma Grading ; Jass, Infiltration Classification according to Jass

Table S3. Subgroup analyses of SARIFA in UICC stage II vs. III

| Group A + B | | | | | |
|---------------------------------------|-------|---------------|---------|--------------------|--|
| Overall survival | HR | 95%CI | p value | p value (log rank) | |
| Stage II (n=340) | 1.299 | 0.696 – 2.424 | 0.411 | 0.409 | |
| Stage III (n=140) | 1.707 | 1.083 – 2.692 | 0.021 | 0.020 | |
| Colon-cancer-specific survival | | | | | |
| Stage II (n=340) | 0.832 | 0.188 – 3.675 | 0.808 | 0.808 | |
| Stage III (n=140) | 2.432 | 1.196 – 4.948 | 0.014 | 0.011 | |
| Metastasis-free survival | | | | | |
| Stage II (n=340) | 1.172 | 0.487-2.817 | 0.724 | 0.723 | |
| Stage III (n=140) | 1.916 | 1.168-3.144 | 0.010 | 0.009 | |

HR: Hazard Ratio of SARIFA positive cases - Reference: SARIFA negative cases; CI: Confidence interval (95%)

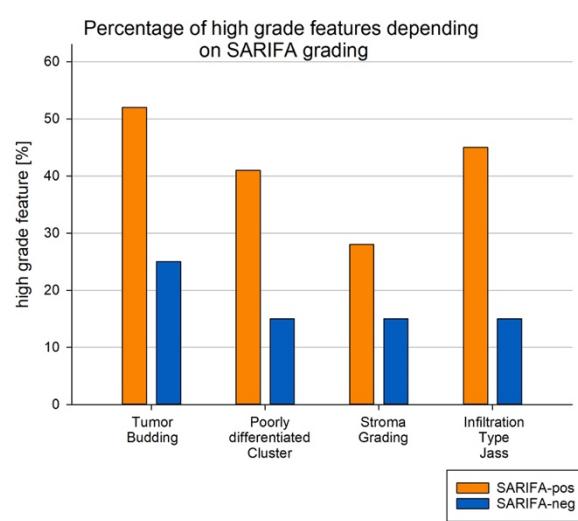


Figure S1 Percentage of high-grade features of morphological biomarkers depending on the SRAIFA grading in group C