抄読会 2021/11/22　　担当　橋元 麻生

# Analysis of tumor microenvironmental features to refine prognosis by T, N risk group in patients with stage III colon cancer (NCCTG N0147) (Alliance)

H.Lee , D.Sha , N.R.Foster , Q.Shi , S.R.Alberts , T.C. Smyrk , F.A. Sinicrope
Annals of Oncology 31.4; 487-494: 2020
https://doi.org/10.1016/j.annonc.2020.01.011

【要旨】
背景：腫瘍浸潤リンパ球(TIL)は、宿主の抗腫瘍免疫反応を反映しており、その密度と局在は大腸がん患者の予後を左右することが明らかになっている。また、Tumor Budding は上皮間葉転換(EMT)との関連が指摘されている。一方 Micropapillary とは、極性が反転した悪性上皮細胞の小さな集団、豊富な好酸球性細胞質、微小乳頭の周囲にラクーア状の空間を形成する引き込みアーチファクトと定義され、EMT との関連が指摘されているほか、KRAS や BRAFV600E との変異頻度の増加や予後の悪化と関連すると報告されている。
対象：NCCTG N0147 に参加した、Stage III の結腸癌患者 1532 名を対象とした。
方法：TIL、Tumor budding、Micropapillary の定量化を行い、DFS からカットオフ値を設定した。個々の病理学的特徴や複合変数と DFS との関連・相対的寄与について、コックス比例ハザードモデルを用いて統計解析を行った。
結果：TIL、Tumor budding、Micropapillary は深達度や N ステージ、MMR の状態により有意に異なっていた(Table 1)。TIL、Budding はそれぞれ DFS と有意に関連していたが、Micropapillary は予後と関連が見られなかった。また、Budding/TIL の複合因子は個々の因子より強固に DFS と相関した(Figure 2)。DFS に対する Budding/TIL の複合因子の相対的寄与は、全体では N ステージに次いで高く、低リスク患者群(T1-T3,N1)では KRAS 変異の有無に次いで 2 番目に高かった。高リスク患者群(T4,N2)では最も高い寄与率を示していた。

【Take home message】
1. Stage III 大腸癌において、TIL と Budding が予後因子として検出された。
2. DFS に対する TIL、Budding の相対的寄与は、N stage に次いで 2 番目に高かった。
3. DFS に対する Budding/ TIL の複合因子の相対的寄与は、低リスク患者群では KRAS に次いで高く、高リスク患者群では最も高かった。

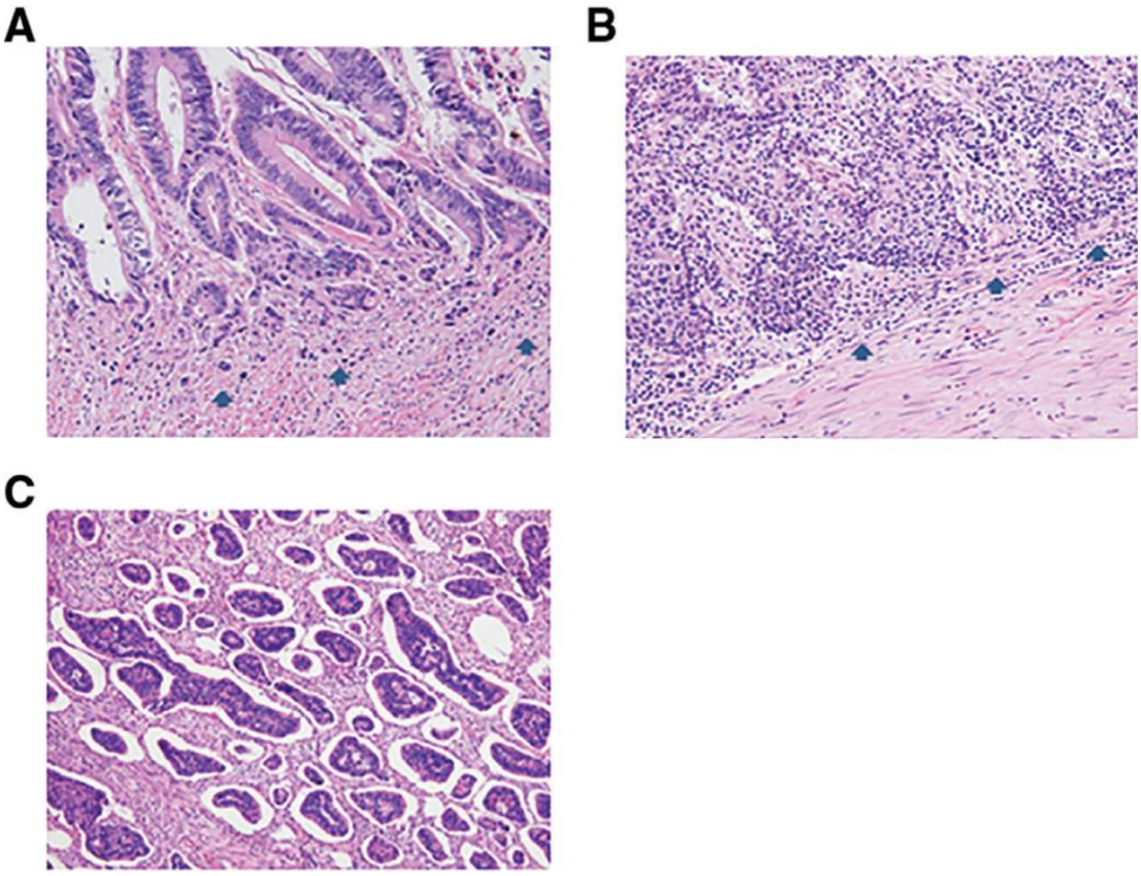


Figure 1. Representative colon adenocarcinomas with invasive margin showing (A) high budding/low TILs or (B) low budding/high TILs, per definitions provided in Methods. (C) Representative colon carcinoma with micropapillary architecture (see Methods). Images display hematoxylin- and eosin-stained tissue sections at x200 magnification (A, B) and x100 magnification (C).

T

**Table 1. Patient characteristics by TIL density, tumor budding and micropapillary features**

| | Low TILs (*N* = 1132) | High TILs (*N* = 400) | *P* value | Low budding (*N* = 699) | High budding (*N* = 833) | *P* value | Micropap absent (*N* = 1205) | Micropap present (*N* = 326) | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | | | 0.0775[a] | | | 0.6057[a] | | | 0.3520[a] |
| Mean (SD) | 58.0 (10.8) | 58.8 (11.8) | | 58.0 (11.3) | 58.4 (10.9) | | 58.3 (11.3) | 57.9 (10.4) | |
| Median | 58.0 | 60.0 | | 59.0 | 59.0 | | 59.0 | 58.0 | |
| Range | (23.0—85.0) | (19.0—86.0) | | (19.0—86.0) | (23.0—85.0) | | (19.0—86.0) | (31.0—5.0) | |
| Sex | | | 0.4937[b] | | | 0.8362[b] | | | 0.7201[b] |
| Female | 535 (47.3%) | 197 (49.3%) | | 336 (48.1%) | 396 (47.5%) | | 579 (48.0%) | 153 (46.9%) | |
| Male | 597 (52.7%) | 203 (50.8%) | | 363 (51.9%) | 437 (52.5%) | | 626 (52.0%) | 173 (53.1%) | |
| Performance status | | | 0.0435[b] | | | 0.8363[b] | | | 0.3079[b] |
| 0 | 843 (74.5%) | 318 (79.5%) | | 528 (75.5%) | 633 (76.0%) | | 906 (75.2%) | 254 (77.9%) | |
| 1/2 | 289 (25.5%) | 82 (20.5%) | | 171 (24.5%) | 200 (24.0%) | | 299 (24.8%) | 72 (22.1%) | |
| T stage | | | 0.0003[b] | | | 0.0002[b] | | | 0.0329[b] |
| T1 or T2 | 145 (12.8%) | 81 (20.3%) | | 129 (18.5%) | 97 (11.6%) | | 190 (15.8%) | 36 (11.0%) | |
| T3 or T4 | 987 (87.2%) | 319 (79.8%) | | 570 (81.5%) | 736 (88.4%) | | 1015 (84.2%) | 290 (89.0%) | |
| N stage | | | 0.0001[b] | | | <0.0001[b] | | | 0.0010[b] |
| N1 (1—3 nodes) | 636 (56.2%) | 270 (67.5%) | | 460 (65.8%) | 446 (53.5%) | | 739 (61.3%) | 167 (51.2%) | |
| N2 (≥4 nodes) | 496 (43.8%) | 130 (32.5%) | | 239 (34.2%) | 387 (46.5%) | | 466 (38.7%) | 159 (48.8%) | |
| Tumor site | | | <0.0001[b] | | | 0.4489[b] | | | 0.3057[b] |
| Right | 534 (47.8%) | 249 (62.9%) | | 349 (50.7%) | 434 (52.6%) | | 624 (52.4%) | 159 (49.2%) | |
| Left | 584 (52.2%) | 147 (37.1%) | | 340 (49.3%) | 391 (47.4%) | | 566 (47.6%) | 164 (50.8%) | |
| Histologic grade | | | 0.0001[b] | | | 0.6028[b] | | | 0.1786[b] |
| Poor/undifferentiated | 880 (77.7%) | 272 (68.0%) | | 530 (75.8%) | 622 (74.7%) | | 916 (76.0%) | 236 (72.4%) | |
| Well/moderate | 252 (22.3%) | 128 (32.0%) | | 169 (24.2%) | 211 (25.3%) | | 289 (24.0%) | 90 (27.6%) | |
| *KRAS* | | | 0.5117[b] | | | 0.0749[b] | | | 0.5306[b] |
| Mutant | 402 (36.1%) | 134 (34.3%) | | 228 (33.2%) | 308 (37.7%) | | 427 (36.1%) | 109 (34.2%) | |
| Wild type | 711 (63.9%) | 257 (65.7%) | | 458 (66.8%) | 510 (62.3%) | | 757 (63.9%) | 210 (65.8%) | |
| *BRAF* | | | <0.0001[b] | | | 0.7374[b] | | | 0.3299[b] |
| Mutant (V600E) | 109 (10.0%) | 89 (23.7%) | | 88 (13.2%) | 110 (13.8%) | | 151(13.1%) | 47 (15.3%) | |
| Wild type | 976 (90.0%) | 286 (76.3 %) | | 577 (86.8%) | 685 (86.2%) | | 1000 (86.9%) | 261 (84.7%) | |
| MMR | | | <0.0001[b] | | | <0.0001[b] | | | <0.0001[b] |
| dMMR | 56 (5.0%) | 97 (24.6%) | | 97 (14.1%) | 56 (6.8%) | | 132 (11.1%) | 21 (6.5%) | |
| pMMR | 1060 (95.0%) | 297 (75.4%) | | 589 (85.9%) | 768 (93.2%) | | 1054 (88.9%) | 303 (93.5%) | |
| Treatment arm | | | 0.2043[b] | | | 0.1358[b] | | | 0.3558[b] |
| FOLFOX | 615 (54.3%) | 232 (58.0%) | | 372 (53.2%) | 475 (57.0%) | | 674 (55.9%) | 173 (53.1%) | |
| FOLFOX + Cetuximab | 517 (45.7%) | 168 (42.0%) | | 327 (46.8%) | 358 (43.0%) | | 531 (44.1%) | 153 (46.9%) | |

dMMR, deficient mismatch repair; micropap, micropapillary features; pMMR, proficient mismatch repair; SD, standard deviation.

[a] Wilcoxon test.

[b] Chi-square test.

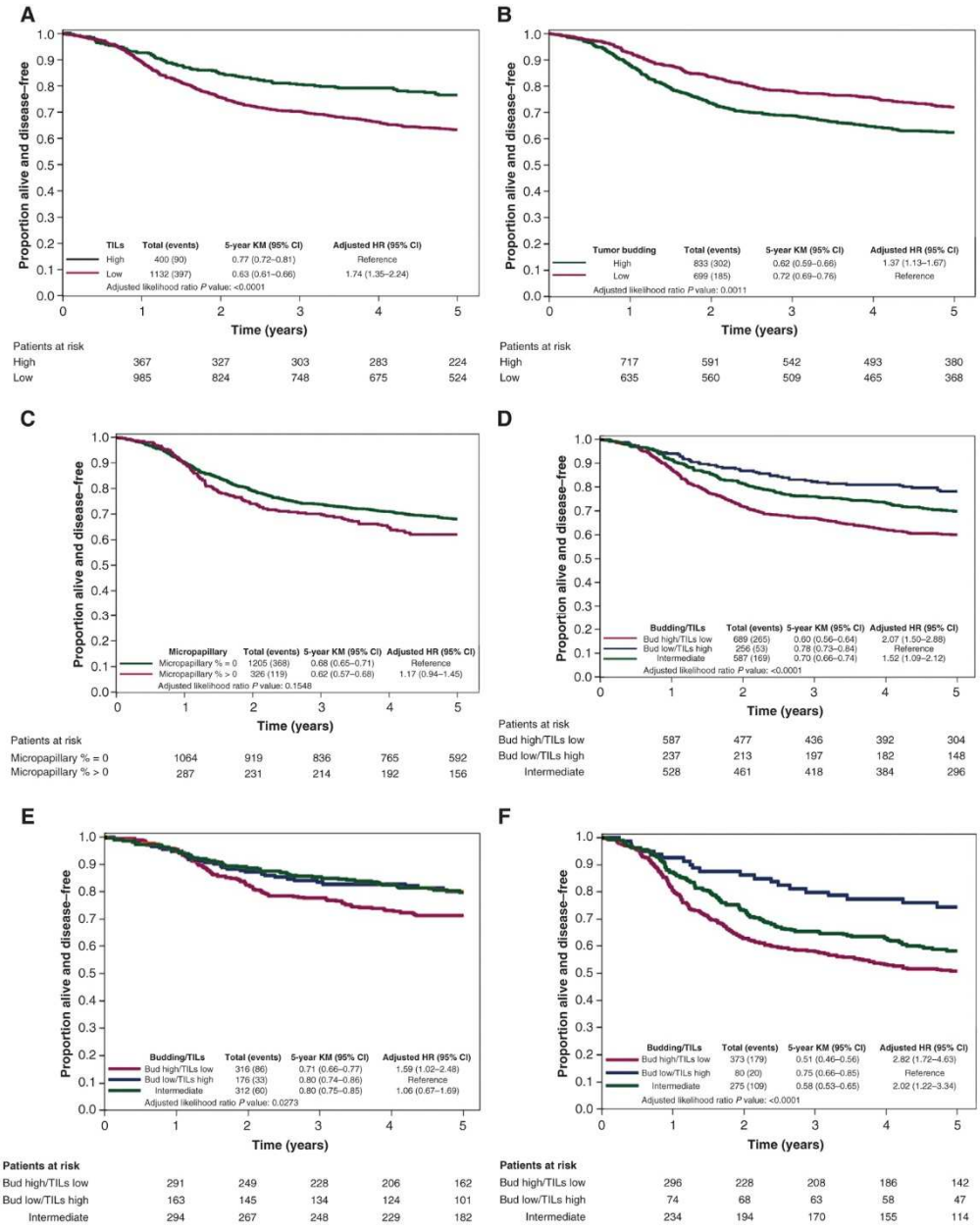


Figure 2. Kaplan-Meier plots of disease-free survival (DFS) in the overall cohort by (A) tumor-infiltrating lymphocytes (TILs), (B) tumor budding, and (C) micropapillary architecture. Also shown is (D), the combined variable of tumor budding/TILs, where the intermediate group includes high budding/high TILs and low budding/low TILs.The tumor budding/TILs combined variable was also analyzed in patients with (E) low-risk (T1-3,N1) and (F) high-risk (T4 and/or N2) stage III tumors.

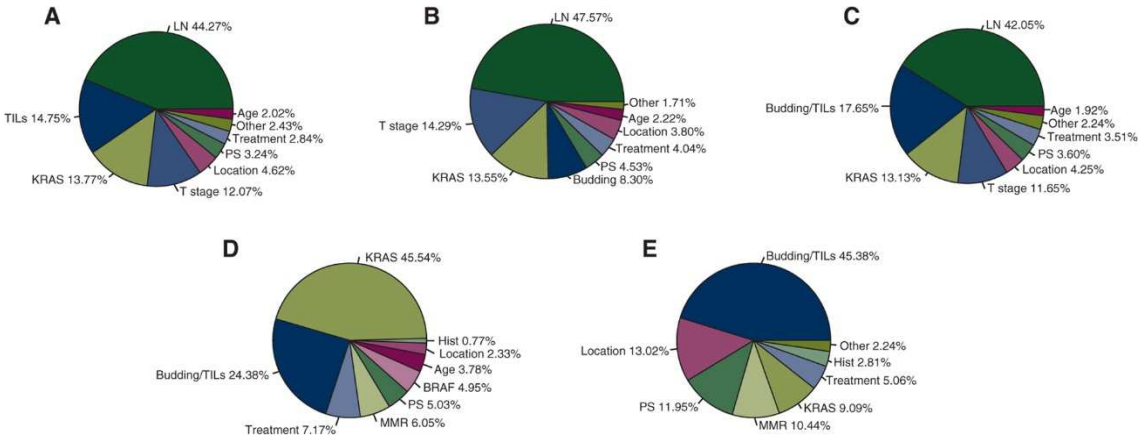


Figure 3. Relative contribution (percent) of (A) tumor-infiltrating lymphocytes (TILs), (B) tumor budding, and (C) the budding/TILs combined variable to disease-free survival (DFS) in the overall cohort of patients with stage III colon cancer. If the relative contribution was less than 1.9% for a given variable, results were pooled into an 'Other' category consisting of (A, B, C) MMR, BRAF, and histologic grade. Among low- and high-risk T, N groups, the relative contribution of the tumor budding/TILs combined variable to patient DFS is shown for (D) low-risk (T1-3 N1) or (E) high-risk (T4 and/or N2) patients. 'Other' includes age and BRAF.