Importance of tumor sampling in transcriptomics–based risk stratification

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Motivation

Intra-tumoral heterogeneity impacts the molecular profiles and results in unstable gene expression-based risk scores. Since the morphological patterns are correlated with gene expression, we explore a morphology-based tumor sampling and its influence on genomic risk scores.

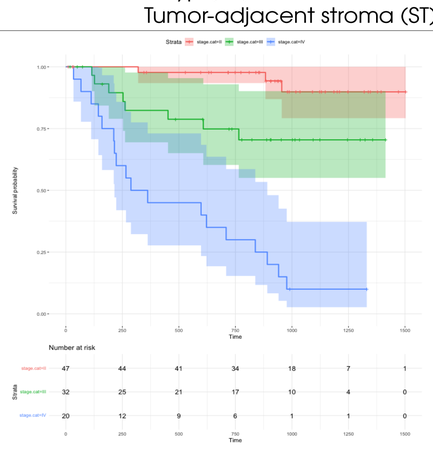
Background

- variability of gene expression signatures across tumor sites has been previously documented (1)
- intra-tumoral heterogeneity (ITH) and tumor sampling strategies impact on consensus molecular subtypes (2,3,4)
- molecular subtypes correlate with tumor morphology patterns (5,6)
- can we use morphology to anchor molecular profiling for risk signatures?

Materials and methods

- 110 tumors: morphological patterns annotated by expert pathologist and macro dissected
- 203 whole-genome good quality expression profiles (Clariom D Affy chips): 30 whole-tumor, 173 morphological parts
- risk scores significance was assessed by time-dependent-AUC index (`timeROC R` package)
- `ESTIMATE` (7) was used to score the stromal and tumoral components of the regions

Age	33-87 (median: 69, mean: 66.6)
Stage	II: 47; III: 32; IV: 20
Grade	1: 11; 2: 52; 3: 36
TNM	T1: 1; T2: 5; T3: 85; T4: 8 N0: 49; N1: 32; N2: 18 M0: 79; M2: 20
Morphological regions	Complex tubular (CT): 52 Desmoplastic (DE): 11 Mucinous (MU): 21 Papillary (PP): 11 Serrated (SE): 41 Solid/trabecular (TB): 9 Tumor-adjacent normal (NR): 17 Polyp (PY): 2 Tumor-adjacent stroma (ST): 9



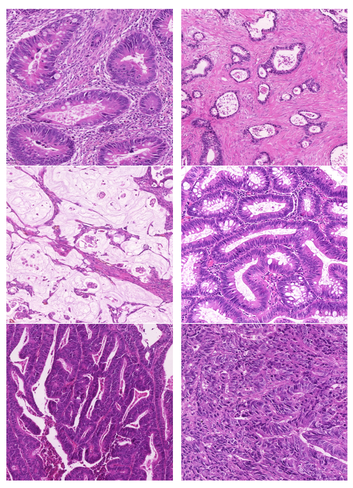


Fig. 2: Morphological patterns: complex tubular; desmoplastic; mucinous; papillary; serrated; solid/trabecular

Results

Risk of recurrence scores: ESCH (10.1200/JCO.2005.00.695); JORI (10.1158/1078-0432.CCR-09-1431); KENN (10.1200/JCO.2011.35.4498); KIM (10/ggcdd6); MA (10.3389/fonc.2020.591739); RS4 (10.3389/fonc.2020.00595); TMRS (10.1016/j.ebiom.2019.03.043); PRGPI (10.1097/MD.0000000000012788); RS12 (10.1186/s12957-020-02116-y); RS6 (10.1186/s12935-018-0724-7)

- `ESTIMATE` scores for stromal component and tumor purity grouped regions into tumor-cell-rich (T) (PP, SE, TB) and tumor-stroma-rich (S) (DE, CT)
- high variability of risk predictions: many predictors disagree in patient risk ranking (Spearman correlation between -0.12 and 0.73)
- in Cox models with whole tumor score and either T-score or S-score indicated the region-based scores were better than whole tumor ($p < 0.05$) in 5 out of 10 cases

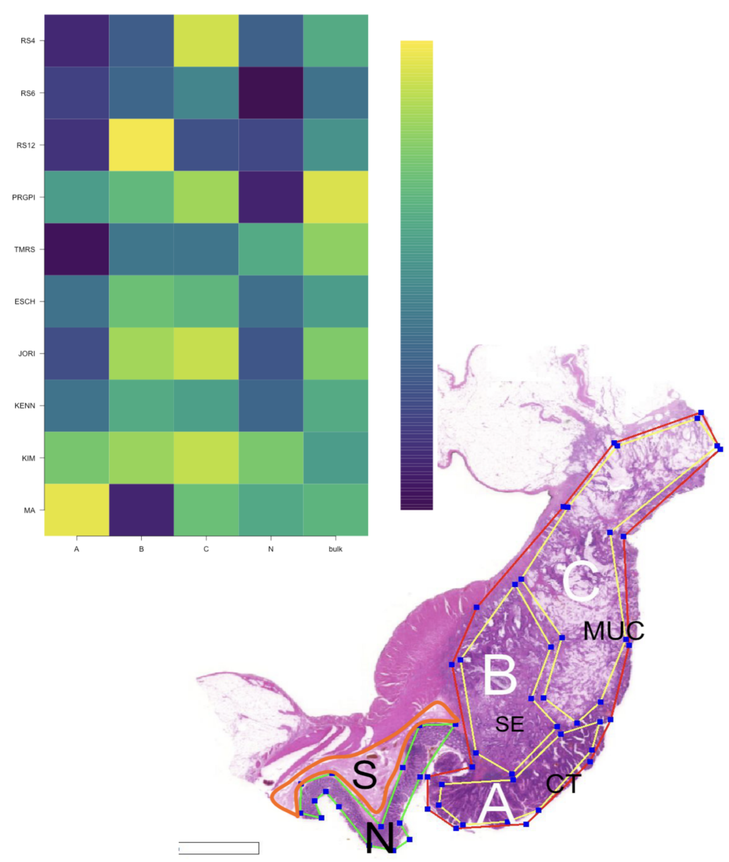


Fig. 3: Intra-tumoral heterogeneity of scores: **rankings** of the various scores computed on morphological regions or whole tumor.

Conclusion and outlook

The prognostic value of the risk scores varies across morphotypes and, in general, can be improved by a more targeted tumor sampling. Each score had a preference for one or the other type of regions (tumor- or stroma-rich), a consequence of their resptective derivation strategies. Consequently, a morphology-guided risk score construction may lead to stronger prognostic performance and a multi-region strategy may prove the most robust.

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Acknowledgments

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