Added prognostic value of tumor-stroma ratio to post-surgery ctDNA in patients with stage III colon cancer

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Biomarkers are needed to guide treatment

Patients with **stage III colon cancer** are routinely treated with resection followed by adjuvant chemotherapy (ACT, fluoropyrimidine + oxaliplatin).

Only ~20% of patients **benefit from ACT**: ~50% are cured by surgery alone and overtreated, while ~30% experience recurrence despite ACT.

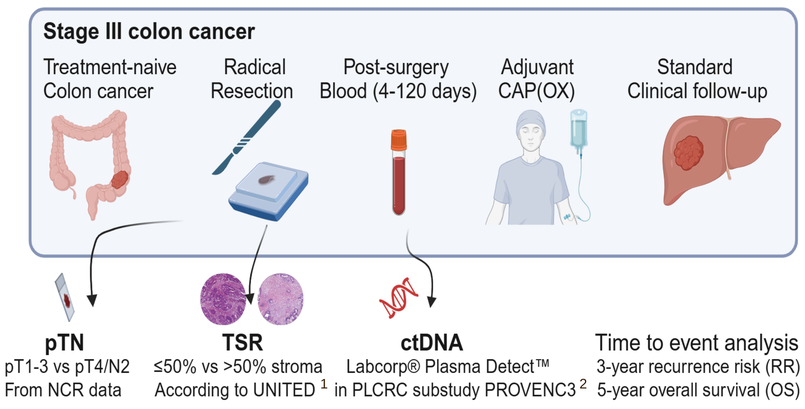
Post-surgery circulating tumor DNA (**ctDNA**) is prognostic of recurrence, but false-negative results necessitate combination with other biomarkers.

Aim of the study

Determine the added value of tumor-stroma ratio (**TSR**) to ctDNA in risk stratification of stage III colon cancer patients treated with ACT**.**

Observational patient cohort

207 patients from Prospectief Dutch ColoRectal Cancer cohort (**PLCRC**):



Concordance between ctDNA and TSR

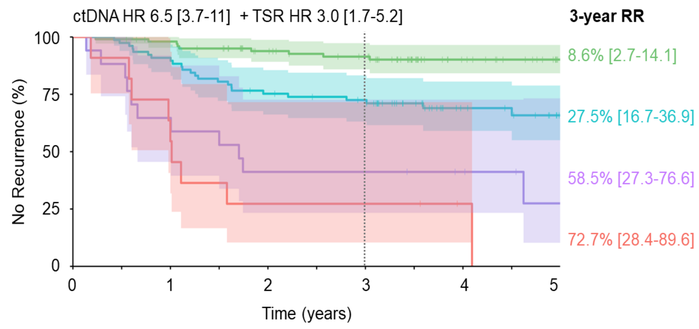
ctDNA was detected in 13%; TTR univariable HR 5.9 [3.3-10].
TSR was stroma-high in 43%; TTR univariable HR 2.7 [1.5-4.7].

	ctDNA-	ctDNA+
Stroma-Low	N=102 (49%)	N=17 (8%)
Stroma-High	N=77 (37%)	N=11 (5%)

Concordance between ctDNA and TSR was low: 55% [48-61].

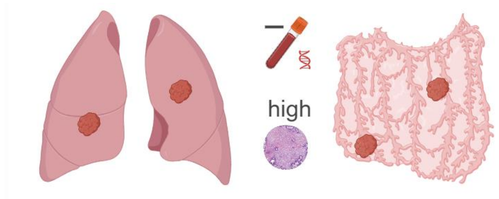
TSR has complementary prognostic value to ctDNA

TSR added prognostic value to ctDNA (LRT p<0.001) in a multivariable Cox model for recurrence, thus improving risk stratification of patients.



TSR helps identify false-negative ctDNA results

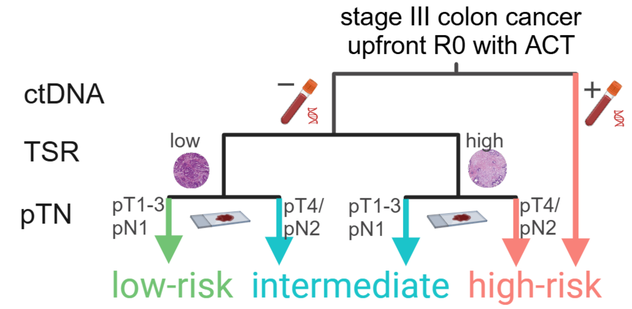
ctDNA did not detect 46% of recurrences, of which 75% were stroma-high. TSR was particularly effective at identifying **low ctDNA shedding sites:** Including metastases to the lungs or peritoneum.



Next to ctDNA and TSR, the conventional clinicopathological **pTN stage** added prognostic value for recurrence (HR 2.6 [1.5-4.6], LRT p<0.001).

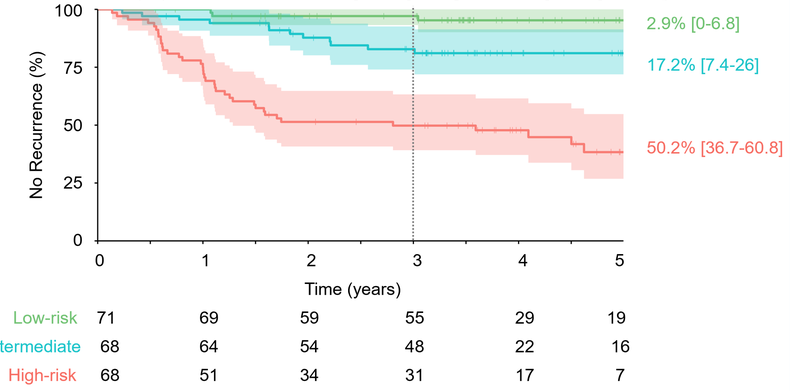
Risk groups were based on ctDNA, TSR and pTN

ctDNA+ was classified as high-risk, as was stroma-high plus pT4/pN2.
ctDNA- plus stroma-low plus pT1-3N1 was classified as low-risk group.

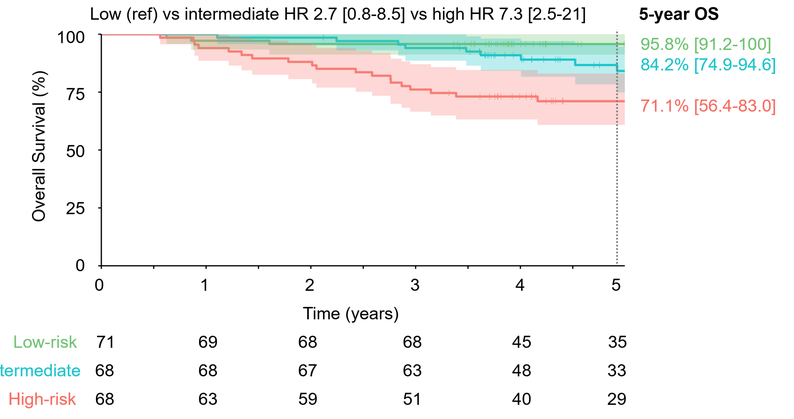


Subgroup with very low risk after ACT

Recurrence within 3 years occurred in <3% in **low-risk** (35% of patients), compared to >50% in the **high-risk** group (33% of total patient cohort).



As for **overall survival**, death within 5 years after resection occurred in <5% in the low-risk group, compared to ~30% in the high-risk group.



Conclusions

Tumor-stroma ratio has added value to post-surgery ctDNA and pTN in **risk stratification** of patients with stage III colon cancer receiving ACT.

A **low-risk** group was identified based on no ctDNA stroma-low pT1-3N1. Upon validation, this group may be spared ACT in the future.

A **high-risk** group was identified on ctDNA, or stroma-high and pT4/N2. This group was not cured by CAP(OX) and requires alternative therapy.

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