321P -A comprehensive predicting model of recurrence in stage III colon cancer from PETACC-8 trial

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Background

- **Intratumor CMS heterogeneity** and **Immunoscore ®** have an important **prognostic impact** in **localized colon cancer** (CC) in addition to T/N stage.
- **Oncotype DX® Colon Cancer Recurrence Score** (*O'Connel et al. JCO 2010*) is a validated supervised signature predictive of recurrence in localized CC, based on:
  - a stromal signature
  - a cell cycle signature
- Many recent studies have shown that **genomic signatures of the tumor microenvironment** (TME) could further refine this stratification

⇨ We established 2 **predictive models of the risk of recurrence** based on known prognostic clinical-pathological features and genomic signatures of the TME and cell cycle from **3'RNAseq** in a large series of patients from **PETACC8 trial** with **stage III CC**.

Material and Methods

- **Patients**

PETACC-8 trial : a phase 3 randomized trial comparing FOLFOX4 + cetuximab and FOLFOX4 in 2,559 patients with stage III CC.

- **Gene expression analyses**

➢ **3'RNAseq of 1,733 FFPE** tissue block sections (QuantSeq 3'mRNA-Seq Kit FWD for Illumina (Lexogen™), **NovaSeq6000** (Illumina))

- **4 genomic signatures of TME and cell cycle**
  - ➢ **Immunoscore Like signature** (*Marisa et al. JNCI 2018*)→ *CD3E,CD3G, CD3D,CD8A* and *PTPRC*
  - ➢ **Oncotype Like score**: derived from the Oncotype DX® Colon Cancer RS:
    . stromal score = *BGN*, *FAP* and *INHBA*
    . cell cycle score =*MKi67*, *MYC* and *MYBL2*

Oncotype Like score = 44 x ((0.15 × stromal score − 0.30 × cell cycle score + 0.15 × gene expression of *GADD45B*)+0.82)

  - ➢ **Macrophage M2 Like signature** (*Combes et al. Cell 2022*)
  - ➢ **CXCL13 expression**

[This work benefited from equipment and services from the iGenSeq core facility, at ICM]

- **dismal CMS combination major.minor** =CMS1.CMS4, CMS4.CMS1, CMS3.CMS4 and CMS1.CMS3 (*Marisa et al. Clin Cancer Res 2021*)

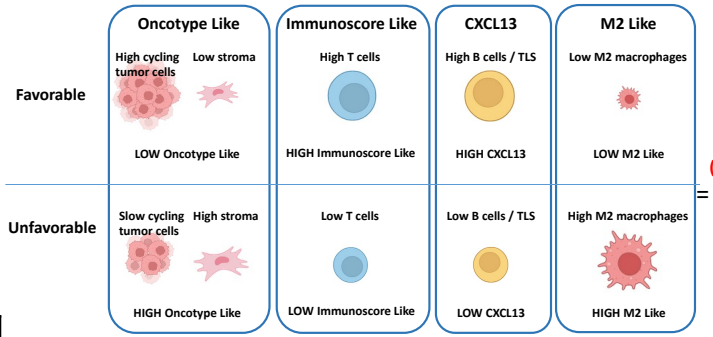
- **Statistical analyses**

2 multivariate Cox proportional hazard models were built using known prognostic variables and signatures of TME/cell cycle for the prediction of recurrence-free survival (RFS).

Results

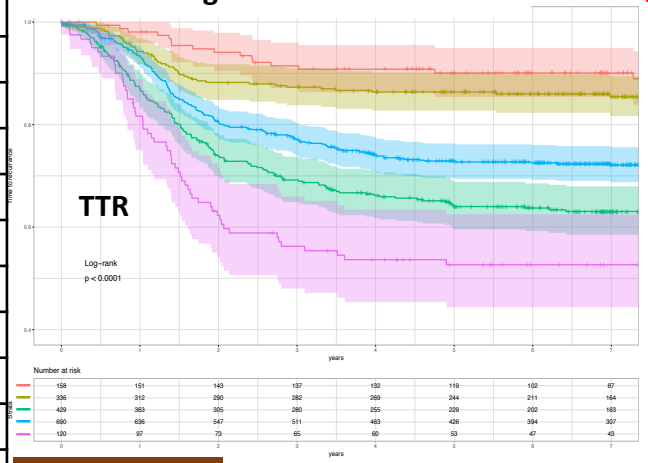
Multivariate model n°1 C-index=0.73

	HR	95% CI	p
Age > 70 y	0.87	0.61-1.24	0.4
Male gender	1.04	0.84-1.28	0.7
WHO-PS 1-2	1.24	0.97-1.58	0.09
Bowel obstruction/perfo	1.23	0.97-1.56	0.09
T4 stage	1.94	1.56-2.42	**<0.001***
N2 stage	2.48	2.01-3.06	**<0.001***
Grade 3-4	1.14	0.89-1.46	0.3
RAS mutation	1.42	1.14-1.78	**0.002***
Interaction pMMR*BRAF mut	2.93	1.14-7.56	**0.03***
BRAF mutation	0.49	0.20-1.19	0.1
pMMR	0.98	0.60-1.59	>0.9
Dismal CMS combination	1.48	1.15-1.90	**0.002***
Signatures of TEM/cell cycle			
Immunoscore Like high vs low	0.66	0.50-0.87	**0.003***
macrophages M2 Like high vs low	1.28	1.0-1.63	**0.05***
Oncotype Like high vs low	1.37	1.08-1.75	**0.01***
CXCL13 high vs low	0.60	0.46-0.77	**<0.001***



IPS score
(Immune Proliferative Stromal)
= **number of unfavorable signatures** (0 to 4)

TTR according to IPS score



IPS
0
1
2
3
4

Multivariate model n°2

Characteristic	HR[1]	95% CI[1]	p-value
T stage			
pT1-3	—	—	
pT4	1.99	1.64, 2.42	**<0.001**
N stage			
pN1	—	—	
pN2	2.26	1.87, 2.73	**<0.001**
Score_IPS			
0	—	—	
1	1.40	0.79, 2.47	0.2
2	2.89	1.74, 4.81	**<0.001**
3	3.92	2.32, 6.63	**<0.001**
4	4.78	2.73, 8.36	**<0.001**
dismal CMS combination	1.51	1.23, 1.86	**<0.001**

[1] HR = Hazard Ratio, CI = Confidence Interval

Conclusion

Signatures related to T cells, B cells/TLS (CXCL13), macrophages M2 infiltration, the stroma and cell cycle provide important information in addition to known prognostic factors for patient stratification with stage III CC.
Combining these diverse variables may help to predict as finely as possible the risk of recurrence, and potentially be exploited in the future for selecting the patients with a poor prognosis and a strong inflammatory cell infiltrate who could benefit from immunotherapy.

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