Independent validation of a prognostic genomic profile (ColoPrint) for stage II colon cancer (CC) patients

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Introduction

Adjuvant therapy is not routinely recommended for stage II (N0) colon cancer patients but should be considered for high-risk patients. In this study we aim to independently validate a genomic profile that was developed to identify high risk patients and can assist in treatment decisions.

Patients and Methods

An 18-gene prognostic profile was developed using whole genome expression data and was validated in an independent cohort of 206 patients and in-silico in public datasets (1). The profile was translated into a robust diagnostic test (ColoPrint). For this study, 135 patients who underwent curative resection (R0) for CC stages II at the Klinikum rechts der Isar from 1987 to 2003 were analyzed. Fresh frozen tissues, clinical parameters, MSI-status and follow-up data for all patients were available. The samples were hybridized and ColoPrint results were determined for all samples blinded from the clinical data.

Schematic Overview of ColoPrint development and validation

Training

- Whole Genome Array
- Training Set (stage I-IV) (n=188) [1]
  Netherlands Cancer Institute, Leiden Medical Center, Slotervaart
- Selection of Final 18-Gene Set & Algorithm

Validation of 18-gene profile

- Standardization of Analytical Methods
- In-silico Validation Study (stage I-III); public datasets (n=322)
  HR = 2.8 (p<0.001) all stages
- Clinical Validation Study I; ICO Barcelona (n=208) [1]
  HR = 3.27 (p=0.015) stage II; HR = 3.1 (P=0.001) all stages
- Clinical Validation Study II; Munich Hospital (n=233)
  HR = 4.1 (p=0.00) stage II, HR = 1.8 (p=0.05) all stages
- PARSC Prospective Study (stage II + III) - *ongoing*
  US, Asian, and European Center (N ~600 stage II) [2]

(1) Salazar et al. (2011) J Clin Oncol 29(1);17-24

(2) PARSC Study Group (2011) ASCO GI Symposiun; Poster Session C, Abstract ID: 602

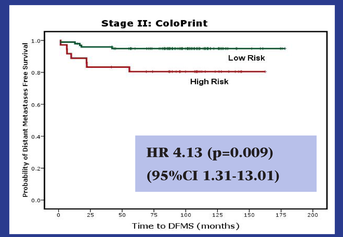
Patient Characteristics and Risk Assessement stage II (n=135)

Variable		Total n=135	%	ColoPrint Low Risk n= 99	74%	ColoPrint High Risk n= 36	26%	p-value
Age (years)	median	65		64.4		66.6		0.773
Follow-up	median	101.4		101.5		103.4		0.905
Gender	Male	77	57	56	56.6	21	58.3	0.854
	Female	58	43	43	43.4	15	41.7	
Localization	Left	78	57.8	59	59.6	19	52.8	0.478
	Right	57	42.2	40	40.4	17	47.2	
Tumor Grade	1, 2	94	69.6	71	71.7	23	63.9	0.382
	3, 4	41	30.4	28	28.3	13	36.1	
LN >12	No	14	10.4	10	10.1	4	11.1	0.865
	Yes	121	89.6	89	89.9	32	88.9	
n LN assessed	median	20		20		20.5		0.836
pT	3	115	85.2	83	83.8	32	88.9	0.465
	4	20	14.8	16	16.2	4	11.1	
Dist. Meta-stasis	No	123	91.1	94	94.9	29	80.6	0.016
	Yes	12	8.9	5	5.1	7	19.4	
Death	No	100	74.1	75	75.8	25	69.4	0.459
	Yes	35	25.9	24	24.2	11	30.6	
Lymphatic +/- Angioinvasion	No	121	89.6	87	87.9	34	94.4	0.352
	Yes	14	10.4	12	12.1	2	5.6	
MSI-status	MSS	101	76.5	70	72.9	31	86.1	0.166
	MSI-H	31	23.5	26	27.1	5	13.9	
Adj Chemo	No	128	94.8	96	97	32	88.9	0.081
	Yes	7	5.2	3	3	4	11.1	
ASCO Risk*	Low	68	50.4	50	50.5	18	50	1.000
	High	67	49.6	49	49.5	18	50	

Results

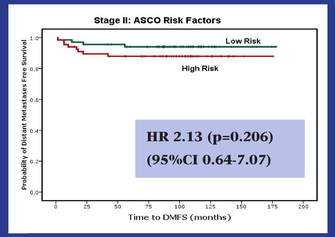
- In the uni- and multi-variate analysis of stage II patients, ColoPrint was the only significant factor to predict the development of distant metastasis with a univariate HR of 4.13 (p=0.009) and a multivariate HR of 4.3 (p=0.013).
- Patients with MSI-H status (n=31) were mostly classified as ColoPrint low risk (86%).
- The identification of high risk stage II patients using clinical parameters from the ASCO recommendations* (T4, High Grade, Perforation and/or less than 12 LN assessed) was not significant (HR 2.13; p=0.2).
- ColoPrint combined with clinical factors might give best risk assessment and this will be analysed in the prospective PARSC trial (2).

Stage II patients classified by ColoPrint



Low Risk (73% of patients)
DMFS 94.9% (95%CI 90.6-99.2)
High Risk (27% of patients)
DMFS 80.5% (95%CI 67.6-93.4)

Stage II patients classified by ASCO risk factors



Low Risk (50.4% of patients)
DMFS 94.1% (95%CI 88.4-99.8)
High Risk (49.6% of patients)
DMFS 87.9% (95%CI 80.1-95.7)

Distant Metastasis Free Survival: Univariate Analysis, Stage II

Variable		HR	95% CI	p-value
ColoPrint	low/ high risk	4.13	1.31 -13.01	**0.009**
Age	continous	1.02	0.97 - 1.07	0.360
Tumor Grade	high vs moderate	1.72	0.55 - 5.43	0.346
Localization	right vs left	1.43	0.46 - 4.43	0.535
Gender	male/ female	0.43	0.12 - 1.58	0.189
# LN assessed	continous	0.97	0.91 - 1.03	0.317
LN > 12	yes/ no	0.55	0.12 - 2.49	0.428
pT	3 vs 4	1.14	0.25 - 5.21	0.865
MSI	MSI-H/ MSS	0.29	0.038 - 2.28	0.21
Lypmh/Angioinvasion	yes/ no	1.78	0.39 - 8.11	0.452
ASCO Risk	High vs Low	2.13	0.64 - 7.07	0.206

Distant Metastasis Free Survival Multivariate Analysis, Stage II

	HR	95% CI	p-value
ColoPrint	4.278	1.35 - 13.50	0.013
ASCO Recommendation*	2.265	0.68 - 7.53	0.183

Conclusions

- ColoPrint is able to predict the development of distant metastasis of stage II colon cancer patients independent of clinical factors and facilitates the identification of patients who may be safely managed without adjuvant chemotherapy.