Tumor Burden Increase at Radiological Disease Progression Associates with Poor Overall Survival in Advanced Colorectal Cancer

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Background

Investigating the association between quantifiable features of tumor burden and survival in advanced cancer patients can uncover elements whose control could potentially influence life expectancy in these patients.

Our aim was to examine how changes in tumor burden, and specifically in sum of longest diameters (SLD) during RECIST-determined progression (i.e. progressive disease, PD) could affect the post-progression survival (PPS) of patients with advanced colorectal cancer (CRC), using proportional-hazards survival models.

Methods & Results

Individual data of metastatic CRC patients under standard-of-care therapy were obtained from 3 clinical studies (accessible via projectdatasphere.org; Tab. 1).

The following factors (covariates) were evaluated as PPS predictors:

Baseline covariates: Gender, age, weight, ECOG performance status, liver/lymph node metastases, histological grade, KRAS mutational status, baseline SLD.

Progression-related covariates:

1. Time to progression (TTP);
2. Nature of the progression (target, non-target, and/or new-lesion PD);
3. Quantitative progression-SLD metrics capturing the tumor burden increase during PD (calculated only in patients uncensored for progression and with measurable tumor burden at RECIST-determined progression).

Clinical study (NCT identifiers)	NCT00272051 NCT00305188	NCT00339183
Treatment line	1st line	2nd line
Number of patients		
Total patients	711	916
All progressing patients (ALL-PD)	459	639
Target-lesion progressing patients (TL-PD)	240	321
Age		
Median, years (range)	62 (22-82)	61 (28-86)
Gender		
Male / Female	429 / 282	348 / 540
Treatment		
FOLFOX	489	-
FOLFIRI	-	457
FOLFIRI + Panitumumab	-	459
Baseline SLD		
Median, cm (range)	10.4 (1-51)	11.2 (2-56)
Time to progression		
Median, months	8.7	4
Overall survival		
Median, months	20.5	12.7

Tab. 1. Patient data characteristics.

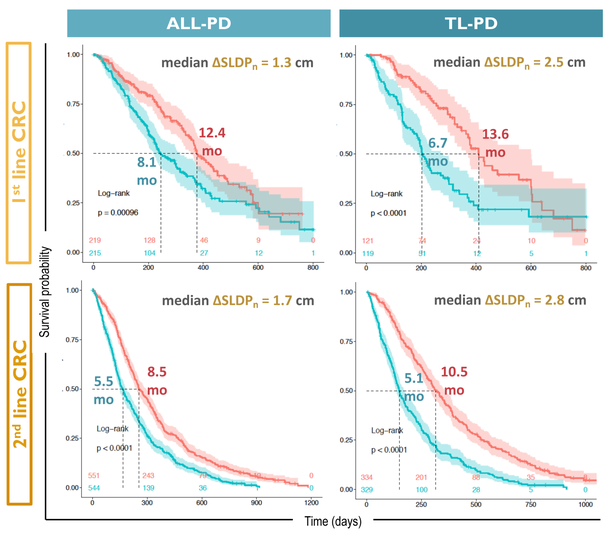
Univariate Analysis

The correlation of progression-associated covariates with survival in different CRC patient groups was examined by (1) univariate Cox proportional-hazards (PH) models, and (2) Kaplan-Meier plots (PPS curve separation assessed by the log-rank test).

The **SLD change from nadir to PD ($\Delta SLDP_n$)** was a significant predictor of PPS in CRC patients under 1st/2nd line treatment (Tab.2)

Patients with small $\Delta SLDP_n$ had a 1.5-2-times longer survival than large-$\Delta SLDP_n$ patients in all groups (Fig. 1)

Fig. 1. Kaplan-Meier survival plots for $\Delta SLDP_n$, dichotomized relative to its median, in patients with any progression type (ALL-PD) or target-lesion progression only (TL-PD) in each dataset. The median values separating the plots are shown for each group, along with corresponding p-values. The median PPS is indicated in each curve.



1st line CRC		ALL-PD Patients			TL-PD Patients		
Covariate		Median	HR	p value	Median	HR	p value
Binary covariates	ProgTL (Target Lesions Progression)	n/a	0.99	0.921	n/a	n/a	n/a
	ProgNL (New Lesions Progression)	n/a	1.19	0.012	n/a	1.30	0.004
	ProgNTL (Non-Target Lesions Progression)	n/a	1.15	0.024	n/a	1.20	0.028
	Gender	n/a	0.94	0.335	n/a	0.86	0.093
	ECOG (Performance Status)	n/a	1.31	$<10^{-3}$	n/a	1.30	0.003
	LV-Mets (Liver Metastasis)	n/a	1.15	0.039	n/a	1.22	0.040
	LN-Mets (Lymph Node Metastasis)	n/a	1.07	0.260	n/a	1.13	0.155
	HG-Low (Histology – Low Grade)	n/a	1.07	0.346	n/a	0.99	0.916
	HG-Med (Histology – Intermediate Grade)	n/a	0.83	0.009	n/a	0.87	0.139
	HG-High (Histology – High Grade)	n/a	1.18	0.012	n/a	1.23	0.022
Continuous covariates	**TTP (Time to Progression)**	231	0.64	$<10^{-3}$	236.5	0.68	$<10^{-3}$
	SLDP (SLD at Progression)	7	1.54	$<10^{-3}$	7.75	1.54	$<10^{-3}$
	$SLDP_{rbl}$ (SLDP relative to baseline)	0.75	1.36	$<10^{-3}$	0.85	1.34	$<10^{-3}$
	$\Delta SLDP_n$ (SLDP change from nadir)	1.3	1.27	$<10^{-3}$	2.5	1.42	$<10^{-3}$
	$\Delta SLDP_m$ (rel. SLDP change from nadir)	0.24	0.77	0.083	0.45	0.65	0.068
	$vSLDP_n$ (SLDP velocity from nadir)	0.34	1.30	0.002	0.76	1.52	$<10^{-3}$
	Age	62	0.83	0.004	64	0.84	0.063
	Weight	70.1	0.89	0.085	70	0.86	0.106
	SLD-BL (SLD at baseline)	10.5	1.33	$<10^{-3}$	10	1.33	$<10^{-3}$

2nd line CRC		ALL-PD Patients			TL-PD Patients		
Covariate		Median	HR	p value	Median	HR	p value
Binary covariates	**ProgTL (Target Lesions Progression)**	1	0.92	0.008	n/a	n/a	n/a
	ProgNL (New Lesions Progression)	0	1.22	$<10^{-3}$	0	1.30	$<10^{-3}$
	ProgNTL (Non-Target Lesions Progression)	1	1.20	$<10^{-3}$	1	1.27	$<10^{-3}$
	Gender	1	1.01	0.716	1	0.97	0.525
	ECOG (Performance Status)	1	1.24	$<10^{-3}$	0	1.19	$<10^{-3}$
	LV-Mets (Liver Metastasis)	1	1.06	0.052	1	1.10	0.015
	KRAS Mutational Status	0	1.08	0.014	0	1.08	0.060
	HG-Low (Histology – Low Grade)	0	0.90	0.001	0	0.91	0.021
	HG-Med (Histology – Intermediate Grade)	1	1.03	0.405	1	0.98	0.612
	HG-High (Histology – High Grade)	0	1.09	0.009	0	1.16	0.001
Continuous covariates	**TTP (Time to Progression)**	120	0.68	$<10^{-3}$	162	0.68	$<10^{-3}$
	SLDP (SLD at Progression)	11.2	1.60	<10-3	11	1.74	<10-3
	$SLDP_{rbl}$ (SLDP relative to baseline)	1.06	1.22	<10-3	1.2	1.26	<10-3
	$\Delta SLDP_n$ (SLDP change from nadir)	1.7	1.28	<10-3	2.8	1.41	<10-3
	$\Delta SLDP_m$ (rel. SLDP change from nadir)	0.23	0.92	0.008	0.33	0.91	0.031
	$vSLDP_n$ (SLDP velocity from nadir)	0.6	1.19	<10-3	0.97	1.24	<10-3
	Age	61	1.00	0.986	61	1.02	0.641
	Weight	73.3	0.91	0.003	73	0.92	0.034
	SLD-BL (SLD at baseline)	11.3	1.37	$<10^{-3}$	10.2	1.44	$<10^{-3}$

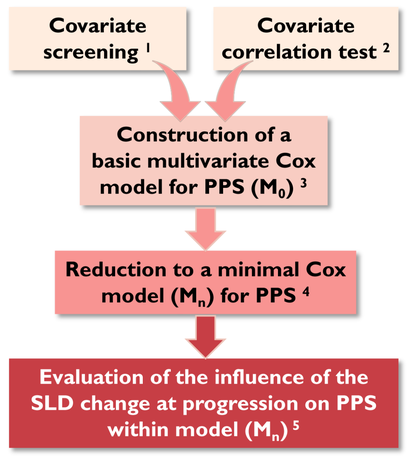
Tab. 2. Univariate Cox regression of PPS on all tested factors. *Progression-SLD metrics (red) and other covariates (black) were tested in all progressing patients (ALL-PD) or only target-lesion-progressing patients (TL-PD) in 1st/2nd line settings. Hazard ratios (HR) and corresponding p values are displayed. Significant covariates (p<0.05) are highlighted.*

- Baseline SLD, ECOG performance status, presence of liver metastasis and high grade histology (poorly differentiated CRC) were also strong PPS predictors (Tab.2).
- Progression-SLD metrics were highly correlated between them, as well as with SLD-BL and ProgTL (not shown). Next, we proceeded to investigate **$\Delta SLDP_n$** as the representing progression-SLD metric in the multivariate model.

Multivariate Models

Multivariate analysis was performed to test whether the change in SLD from nadir to PD is an independent predictive factor for PPS. Thus, optimally sparse Cox PH models for PPS were built for each dataset and patient group, and the effect of adding $\Delta SLDP_n$ was tested through HR, p value and the model Akaike information criterion (AIC) value (Fig. 2).

Fig. 2. Approach for the multivariate model development.



1. Only factors having a p value of <0.1 in the univariate Cox model in both patient subgroups (ALL-PD, TL-PD) were selected; progression-SLD metrics were excluded altogether
2. Highly correlated factors were reduced
3. Model M_0 was constructed by regression of PPS on all the selected covariates, without progression-SLD metrics
4. The minimal model M_n was constructed by backward stepwise elimination of covariates, with a p value threshold of 0.05
5. The importance of $\Delta SLDP_n$ (or the residual, derived by its regression on other covariates) when added to the minimal model M_n was evaluated by its HR, significance (p value) and change in AIC

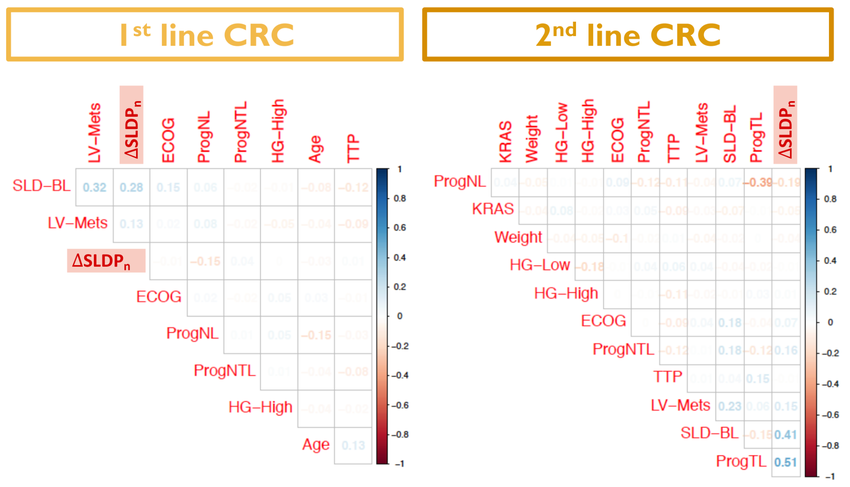
The SLD change from nadir to PD ($\Delta SLDP_n$) remained an important PPS predictor in multivariate models controlling for other prognostic factors, including ECOG, TTP, KRAS, etc. (Tab. 3), and its addition improved the model AIC in every patient group and treatment line

The predictive power of $\Delta SLDP_n$ is apparent even in models with correlated covariates, e.g. SLD-BL, as seen in models containing the residual of its regression on all other factors (Tab. 3)

In the 2nd line cohort, SLD-BL (baseline tumor size at 2nd line onset, at the end of 1st line) was the most significant PPS predictor (Tab. 3), stressing the importance of the SLD change at progression during 1st line therapy for survival.

The factor $\Delta SLDP_n$ strongly correlated with SLD-BL, ProgTL and ProgNL (Fig. 3). These correlations were weighed out by regressing $\Delta SLDP_n$ on other factors and using the residuals from this regression, res.$\Delta SLDP_n$, as an added survival predictor.

Fig. 3. Correlation matrix for significant PPS covariates (p<0.1 in the univariate Cox regressions in ALL-PD and TL-PD patients; Tab. 2).



Tab. 3. Multivariate Cox regressions for 1st/2nd line-treated CRC patients with progression of any type (ALL-PD) or target-lesion progression (TL-PD). Covariates are listed alongside their HR values (and 95% confidence interval), and significance.

ALL-PD Patients

1st line CRC	Minimal model		Minimal model + $\Delta SLDP_n$		Minimal model + residual of $\Delta SLDP_n$	
Covariate	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
ProgNTL	1.14 (1.01 - 1.28)	0.04	1.15 (1.02 - 1.30)	0.03	1.16 (1.03 - 1.31)	0.018
ECOG	1.32 (1.17 - 1.50)	$<10^{-3}$	1.36 (1.19 - 1.55)	$<10^{-3}$	1.34 (1.18 - 1.53)	$<10^{-3}$
TTP	0.64 (0.54 - 0.74)	$<10^{-3}$	0.61 (0.52 - 0.72)	$<10^{-3}$	0.61 (0.52 - 0.72)	$<10^{-3}$
SLD-BL	1.31 (1.17 - 1.46)	$<10^{-3}$	1.26 (1.11 - 1.42)	$<10^{-3}$	1.33 (1.19 - 1.49)	$<10^{-3}$
$\Delta SLDP_n$	-	-	**1.21 (1.06 - 1.38)**	**0.004**	-	-
res. $\Delta SLDP_n$	-	-	-	-	**1.2 (1.06 - 1.36)**	**0.004**

2nd line CRC	Minimal model		Minimal model + $\Delta SLDP_n$		Minimal model + residual of $\Delta SLDP_n$	
Covariate	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
ECOG	1.14 (1.07 - 1.22)	$<10^{-3}$	1.14 (1.07 - 1.22)	$<10^{-3}$	1.14 (1.07 - 1.22)	$<10^{-3}$
KRAS	1.14 (1.07 - 1.22)	$<10^{-3}$	1.15 (1.08 - 1.23)	$<10^{-3}$	1.15 (1.08 - 1.23)	$<10^{-3}$
TTP	0.66 (0.61 - 0.72)	$<10^{-3}$	0.66 (0.61 - 0.71)	$<10^{-3}$	0.66 (0.61 - 0.71)	$<10^{-3}$
Weight	0.89 (0.83 - 0.95)	$<10^{-3}$	0.90 (0.84 - 0.96)	0.001	0.89 (0.83 - 0.95)	$<10^{-3}$
SLD-BL	1.43 (1.34 - 1.52)	$<10^{-3}$	1.36 (1.27 - 1.46)	$<10^{-3}$	1.46 (1.36 - 1.56)	$<10^{-3}$
$\Delta SLDP_n$	-	-	**1.18 (1.11 - 1.25)**	**$<10^{-3}$**	-	-
res. $\Delta SLDP_n$	-	-	-	-	**1.18 (1.11 - 1.25)**	**$<10^{-3}$**

TL-PD Patients

1st line CRC	Minimal model		Minimal model + $\Delta SLDP_n$		Minimal model + residual of $\Delta SLDP_n$	
Covariate	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
ProgNTL	1.32 (1.11 - 1.59)	0.002	1.31 (1.10 - 1.57)	0.003	1.36 (1.13 - 1.63)	0.001
ECOG	1.35 (1.13 - 1.62)	$<10^{-3}$	1.37 (1.15 - 1.64)	$<10^{-3}$	1.36 (1.14 - 1.63)	$<10^{-3}$
TTP	0.63 (0.51 - 0.78)	$<10^{-3}$	0.64 (0.52 - 0.79)	$<10^{-3}$	0.63 (0.51 - 0.78)	$<10^{-3}$
SLD-BL	1.37 (1.18 - 1.60)	$<10^{-3}$	1.16 (0.93 - 1.44)	0.19	1.37 (1.18 - 1.60)	$<10^{-3}$
$\Delta SLDP_n$	-	-	**1.32 (1.05 - 1.66)**	**0.02**	-	-
res. $\Delta SLDP_n$	-	-	-	-	**1.24 (1.04 - 1.48)**	**0.02**

2nd line CRC	Minimal model		Minimal model + $\Delta SLDP_n$		Minimal model + residual of $\Delta SLDP_n$	
Covariate	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
ECOG	1.12 (1.03 - 1.22)	0.007	1.12 (1.03 - 1.22)	0.01	1.12 (1.03 - 1.21)	0.01
KRAS	1.15 (1.05 - 1.25)	0.001	1.15 (1.06 - 1.25)	0.001	1.15 (1.06 - 1.26)	0.001
TTP	0.62 (0.56 - 0.69)	$<10^{-3}$	0.64 (0.58 - 0.71)	$<10^{-3}$	0.63 (0.57 - 0.69)	$<10^{-3}$
SLD-BL	1.62 (1.49 - 1.77)	$<10^{-3}$	1.49 (1.33 - 1.67)	$<10^{-3}$	1.63 (1.49 - 1.77)	$<10^{-3}$
$\Delta SLDP_n$	-	-	**1.12 (1.01 - 1.24)**	**0.02**	-	-
res. $\Delta SLDP_n$	-	-	-	-	**1.12 (1.01 - 1.24)**	**0.03**

Conclusions and Implications

- The **increase in tumor size from nadir to progression ($\Delta SLDP_n$) is a survival predictor in CRC patients;** its predictive power appears independent of the treatment line and drug applied to the patients.
- $\Delta SLDP_n$ is an independent significant predictor of survival, also when considered relatively to other disease predictors.
- This complements our past discovery that survival in metastatic non-small cell lung cancer is correlated with $\Delta SLDP_n$ [1], suggesting the **cross-indication prognostic value of this factor**.
- A potential implication: **identification of impending progression at the right time,** when the tumor increase is still small, **could enable oncologists to effectively extend the patient's survival** (e.g. by an earlier switch to next-line therapy). This possibility must be prospectively tested.

References: [1] Kogan Y, Elishmereni M, Taub E, Agur Z. Increase in tumor burden at disease progression as a predictor of survival in advanced NSCLC patients. J Clin Oncol 36, 2018 (suppl; abstr e21114).

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