

# Clinical and molecular determinants of extrahepatic disease progression (ePD) in initially unresectable, liver-limited metastatic colorectal cancer (mCRC).

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## Background

In the last years, the availability of active upfront systemic regimens, the development of surgical techniques and the diffusion of other locoregional treatments increased the therapeutic options for mCRC patients with liver-limited disease.

Kopetz et al. *J Clin Oncol* 2009; Cremolini et al. *Eur J Cancer* 2017; Wei et al. *PLOS One* 2014; Ruers et al. *Ann Oncol* 2012

Estimating the likelihood to develop extra-hepatic metastases may affect clinicians' attitudes towards locoregional procedures. No tools to predict the probability of ePD of initially liver limited mCRC are currently available.

## Methods

We retrospectively analysed a cohort of 225 patients with initially unresectable liver-limited disease, treated from January 2004 to December 2017 with first-line doublets or triplet plus a biologic agent at two Italian Institutions. Information about baseline clinical, pathological and molecular features, treatments received and metastatic sites from the diagnosis of mCRC to death or last follow up were collected. The impact of baseline characteristics and treatments received on extra-hepatic progression-free survival (ePFS) was assessed in uni- and multi-variable models.

## Results

Overall, 52 (23%) patients were ePD-free and 173 (77%) experienced ePD which occurred within 1, 2 or 3 years from the diagnosis of mCRC in 20%, 63%, and 86% of patients, respectively. Globally, 164 (73%) patients underwent a secondary liver resection at some point of their disease history, and 66 (40%) of them underwent a subsequent locoregional treatment. Among 164 resected patients, 118 (72%) experienced ePD, occurring within 1, 2 or 3 years from resection in the 43%, 71%, and 91% of cases, respectively.

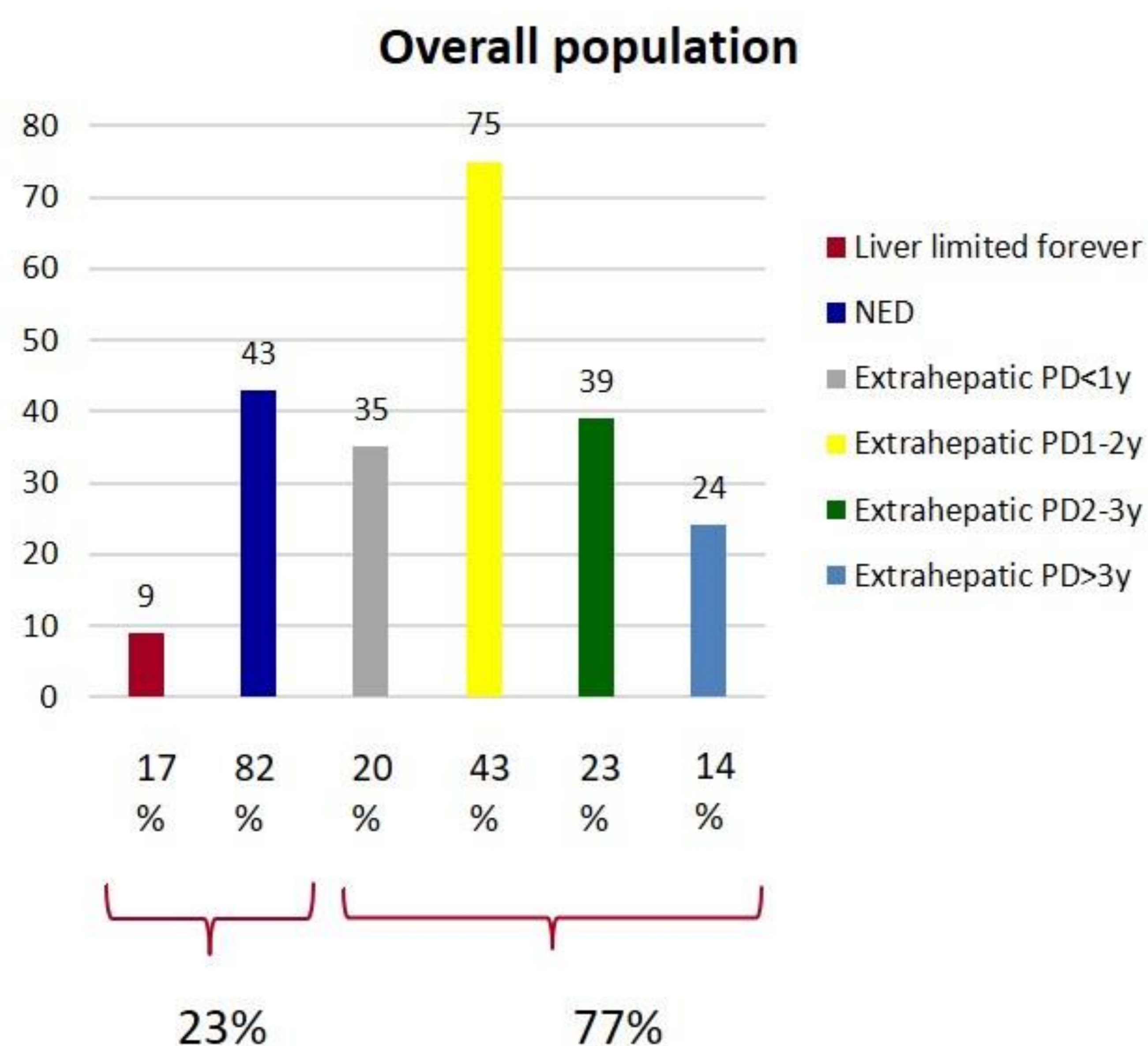


Figure 1. ePD distribution in overall population

## Overall population

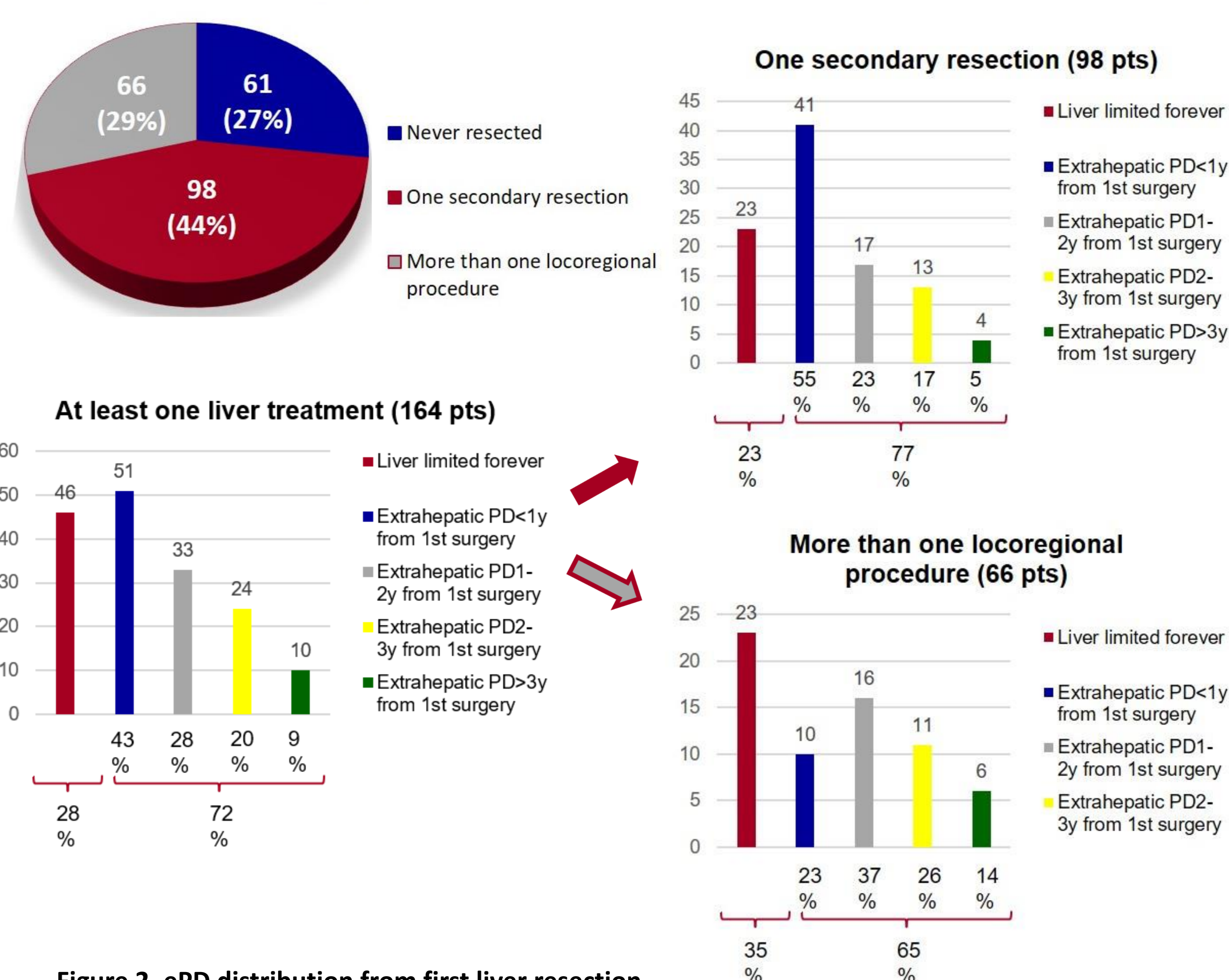


Figure 2. ePD distribution from first liver resection

Age < 70 years, ECOG performance status (PS) 0, < 4 liver metastases, longest diameter of liver lesions < 30 mm, the involvement of < 6 liver segments and secondary resection were significantly associated with prolonged ePFS. In the multivariable model, ECOG PS (p=0.022), number (p=0.011) and diameter (p=0.005) of liver metastases and secondary liver resection (p=0.006) were still associated with ePFS. In the subgroup of analysed patients (N=35), microsatellite instability was associated with shorter ePFS (p=0.03). In the subgroup of patients who did not undergo metastases' resection in their disease history (N=61), ECOG PS 0 (p=0.024), longest diameter of liver lesions < 30 mm (p=0.011) and left-sidedness (p=0.081) were independently associated with longer ePFS.

Characteristics	Univariable analyses			Multivariable analyses		
	HR	95% CI	p value	HR	95% CI	p value
Age ≥ 70 yrs vs < 70 yrs	1.43	0.93-2.18	0.07	1.02	0.99-1.04	0.12
ECOG PS 1 vs 0	1.45	0.89-2.33	0.08	2.04	1.11-3.72	0.02
Synchronous vs metachronous	1.31	0.87-1.98	0.24	-	-	-
Resected primary tumor vs unresected	0.84	0.61-1.15	0.26	-	-	-
Left vs right primary	0.89	0.64-1.26	0.52	-	-	-
Nodal involvement vs no involvement	1.55	1.08-2.23	0.03	1.48	0.91-2.40	0.12
Baseline CEA level > 200 vs ≤ 200 ng/mL	1.19	0.80-1.77	0.37	-	-	-
Number of liver metastases ≥ 4 vs < 4	1.67	1.22-2.29	0.003	1.83	1.15-2.90	0.01
Liver mts max diameter > 30 vs ≤ 30 mm	1.35	0.96-1.86	0.09	1.98	1.23-3.20	0.005
Bilobar involvement yes vs no	1.14	0.82-1.58	0.44	-	-	-
Liver involvement > 6 vs ≤ 6 segments	1.40	0.94-2.09	0.06	0.69	0.36-1.33	0.27
RAS/RAF mutation vs RAS/RAF wild type	1.11	0.82-1.51	0.67	-	-	-
MSI High vs MSI low/MSS	2.41	0.42-13.88	0.03	.*	.*	.*
Triplet vs doublet induction	1.20	0.89-1.62	0.22	-	-	-
Liver secondary resection	0.39	0.26-0.59	< 0.001	0.37	0.21-0.65	< 0.001

Table 1. Uni- and multivariable analyses for ePFS

\*Too small sample size for multivariable model (N=35)

## Conclusions

In this contemporary cohort, the vast majority of mCRC patients with initially unresectable liver-limited disease underwent surgical procedures (73%) and further locoregional interventions (40%) in their disease history. ECOG PS, number and diameter of liver metastases, and secondary liver resections independently predict ePFS. These factors could help physicians in personalizing the intensity and aggressiveness of liver directed treatments in mCRC patients with initially unresectable liver-limited disease.