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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 15%, 49%, and 66% of patients, respectively. Globally, 164 (73%) patients underwent a secondary liver resection at some point of their disease history, and 54 (33%) of them underwent a subsequent locoregional treatment.

Figure 1. Description of the overall study population (A) and of ePDs' distribution in the overall population (B), in the subgroup of patients undergoing one (C) or more than one (D) liver resection.

Age over 70 years (SHR 1.50, 95% CI, 1.04-2.18; p=0.03), nodal involvement at diagnosis (SHR 1.50, 95% CI 1.01-2.22; p=0.04) and more than 4 liver metastases at baseline (SHR 1.79, 95% CI 1.28-2.52; p=0.001) were significantly associated with higher risk for ePD. On the contrary, undergoing a liver resection was associated with lower risk of ePD (SHR 0.38, 95% CI 0.26-0.56; p=0.001). In the multivariable model, number of liver metastases (SHR 1.63, 95% CI 1.12-2.36; p=0.01) and liver resections (SHR 0.43, 95% CI 0.29-0.63; p=0.001) were still associated with ePD.

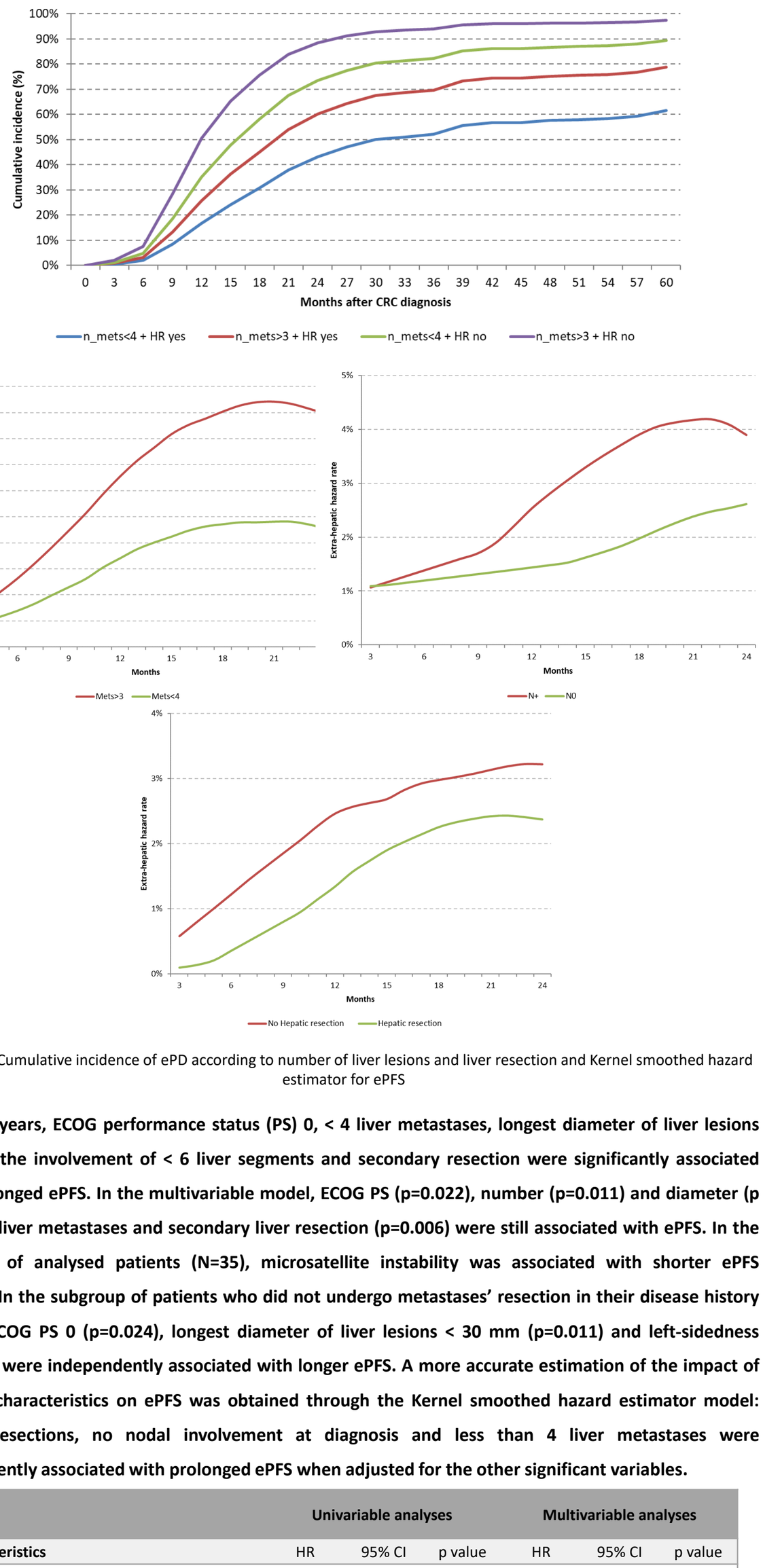

Figure 2. Cumulative incidence of ePD according to number of liver lesions and liver resection and Kernel smoothed hazard estimator for ePFS

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. A more accurate estimation of the impact of baseline characteristics on ePFS was obtained through the Kernel smoothed hazard estimator model: hepatic resections, no nodal involvement at diagnosis and less than 4 liver metastases were independently associated with prolonged ePFS when adjusted for the other significant variables.

	Univariable analyses			Multivariable analyses		
Characteristics	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 ≤ 6segments	**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 (33%) 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.

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