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RESEARCH PAPER

Histopathological growth patterns of resected non-colorectal, non-neuroendocrine liver metastases: a retrospective multicenter study

Yannick Meyer[1] · Ali Bohlok[2] · Diederik Höppener[1] · Boris Galjart[1] · Michail Doukas[3] · Dirk J. Grünhagen[1] · Anaïs Labar[2] · Valerio Lucidi[4] · Peter B. Vermeulen[5] · Cornelis Verhoef[1] · Vincent Donckier[2]

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Abstract

Background Distinct Histopathological Growth Patterns can be identified in liver metastases from melanoma, breast and colorectal cancers. For each of these distinct liver metastasis types the HGP has proven a biomarker for survival after partial hepatectomy, with the desmoplastic type marking favourable prognosis. Whether HGPs can be considered a pan-cancer phenomenon remains unknown. This study therefore evaluates the presence of HGPs and their prognostic value across non-colorectal non-neuroendocrine liver metastases.

Methods A retrospective multicentre cohort study was performed in patients who underwent curative intent resection of non-colorectal non-neuroendocrine liver metastasis. HGPs were assessed on Haematoxylin and Eosin slides according to consensus guidelines and classified as desmoplastic or non-desmoplastic. Overall- and recurrence-free survival were evaluated using Kaplan–Meier and multivariable Cox regression analysis.

Results In total, 132 patients with liver metastasis from 25 different tumour types were eligible for analysis, of which 26 (20%) had a desmoplastic HGP. Five-year OS and RFS (95%CI) were 53% (36–78%) versus 40% (30–53%), and 33% (19–61%) versus 15% (9–27%) for patients with desmoplastic compared to non-desmoplastic metastases, respectively ($p = 0.031$ & $p = 0.004$). On multivariable analysis (adjusted HR [95%CI]) a desmoplastic HGP was prognostic for both OS (0.46 [0.25–0.86]) and RFS (0.38 [0.21–0.69]).

Conclusions This study demonstrates that HGPs apply to liver metastases across a wide variety of primary tumour origins. They hold a prognostic value in these cases, suggesting that HGPs could represent a pan-cancer biomarker for survival after surgical resection of liver metastases.

Keywords Liver metastases · Resection · Prognosis · Histopathological growth patterns · Survival

Yannick Meyer and Ali Bohlok have equally contributed to this study.

✉ Vincent Donckier
vincent.donckier@bordet.be

1 Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

2 Department of Surgical Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

3 Department of Pathology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

4 Department of Abdominal Surgery, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

5 Translational Cancer Research Unit (GZA Hospitals and University of Antwerp), Antwerp, Belgium

Introduction

Histopathological Growth Patterns (HGPs) are a pathology-based parameter that describes the tumour-liver interface. Assessment of HGPs is performed using light-microscopy of haematoxylin-and-eosin (H&E) stained slides of liver tumours and has been standardized in international consensus guidelines [1]. The morphological subtypes can be grouped into pure desmoplastic, and non-desmoplastic HGP (Fig. 1). The desmoplastic HGP (dHGP) is characterized by a rim of desmoplastic stroma separating the metastasis from the surrounding liver tissue, without contact between the tumour cells and surrounding hepatocytes. The metastases with a desmoplastic HGP do not mimic the liver architecture. The non-desmoplastic HGP (non-dHGP) contains two

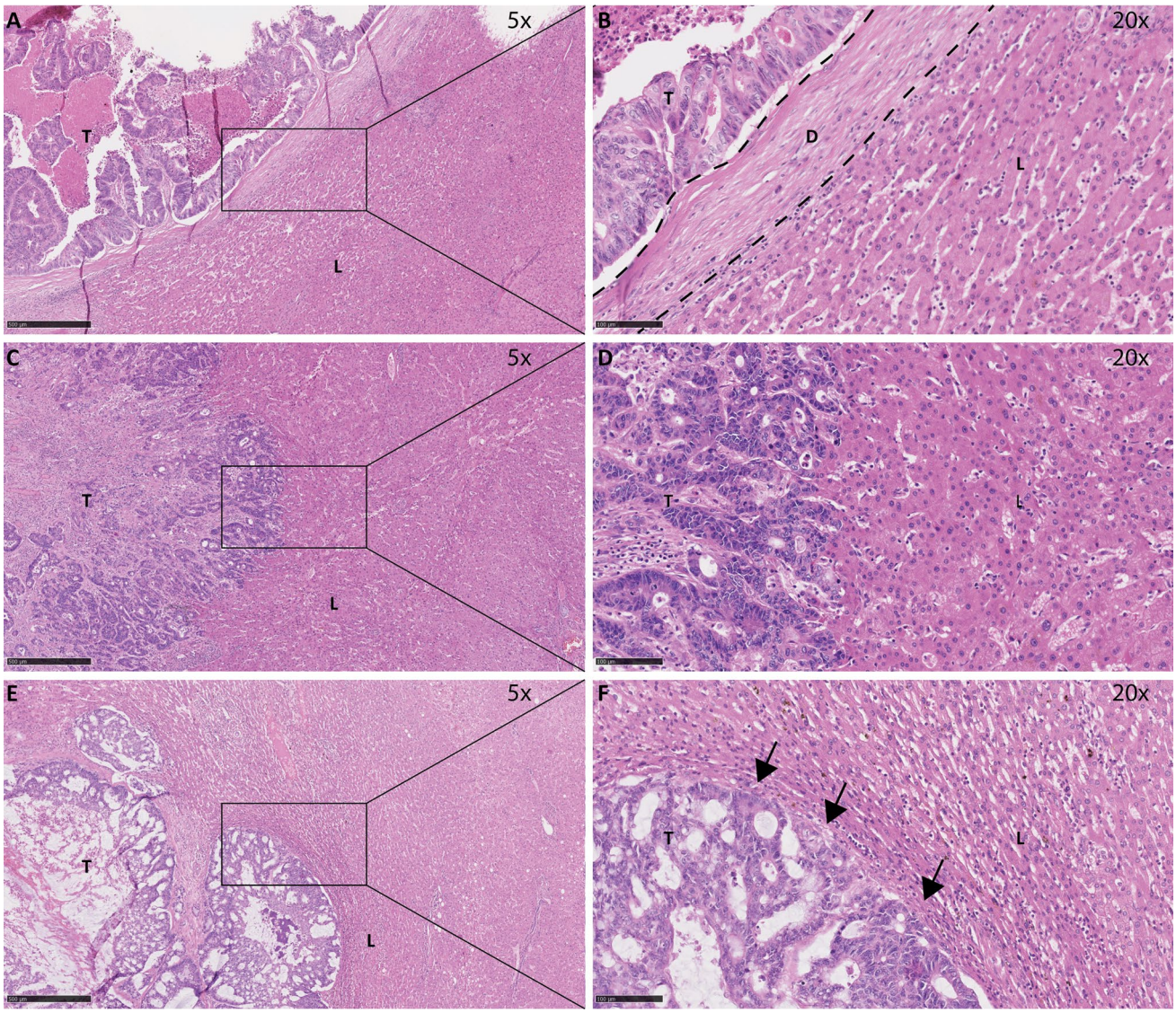

Fig. 1 Morphological phenotypes of the different histopathological growth patterns (HGPs) in CRLM at 5 × and 20 × magnification; **A** & **B** Desmoplastic HGP; **C**-FNon-desmoplastic HGP (**C** & **D** Replacement HGP, E&F Pushing HGP). Scale bars represent 500 um. *T* Tumour, *L* Liver, *D* Desmoplastic rim, The dotted lines in **E** demarcate the desmoplastic rim; The arrows in **F** highlight direct contact of hepatocytes and tumour cells in pushing HGP

main subgroups. The replacement HGP is characterized by tumour cells replacing the hepatocytes at the tumour-liver interface. There is direct contact between tumour cells and hepatocytes. Replacement of hepatocytes in the liver cell plates results in conservation of the liver architecture within the metastasis. In the rare pushing HGP, the liver plates run parallel to the circumference of the metastasis. There is no replacement of hepatocytes by tumour cells and there is no desmoplastic stroma separating the metastasis from the surrounding liver [2].

The HGPs have been studied most extensively in colorectal cancer liver metastases (CRLM). In patients with pure desmoplastic CRLM, superior overall (OS) and recurrence-free survival (RFS) after surgical resection were observed when compared to patients with non-desmoplastic metastases (i.e. any replacement or pushing HGP component) [3, 4]. In addition, HGPs are not only of prognostic, but also of predictive value. Adjuvant systemic chemotherapy seems only beneficial in patients with a non-desmoplastic HGP, and HGPs have been demonstrated to be predictive with regard to response to anti-angiogenic therapy [5, 6].

Resection of liver metastases from non-colorectal cancers and non-neuroendocrine tumours is less common [7–9]. The group of patients with non-colorectal non-neuroendocrine liver metastases (NCRNNELM) is highly heterogeneous from both a biological and a therapeutic

management perspective. Given this heterogeneity and the lack of clear indications for surgery, a pan-cancer approach to aid prognostication could be considered for patients with NCRNNELM. As HGPs have been described in several liver tumours so far, they represent a candidate pan-cancer biomarker for this group of patients. By studying HGPs in patients who underwent resection of NCRNNELM, this study aims to investigate whether HGPs can be identified across liver metastases from various origins, and whether a desmoplastic HGP is a marker for superior survival in these patients.

Methods

A multicentre retrospective cohort study was performed at the Erasmus MC Cancer Institute (Rotterdam, the Netherlands), the Institut Jules Bordet (Brussels, Belgium) and the Hôpital Erasme (Brussels, Belgium). Patients who underwent curative intent surgical resection for NCRNNELM were identified from the respective centres electronic records. The inclusion period ranged from January 2000 to December 2019. Treatment was considered intentionally curative if all preoperatively identified intra- and extrahepatic lesions were treated via resection or a combination of resection and ablation.

Clinicopathological data for patient, primary tumour, and metastasis characteristics as well as RFS were retrieved from the digital medical records. The municipal population register was used in addition to the digital medical records to collect data on patient survival. The Adam score, a multivariable risk model to predict long-term survival after resection of non-colorectal non-neuroendocrine liver metastases, was calculated for all patients [10, 11]. The score ranges from zero to ten, with higher scores indicating poorer prognosis, and includes the following clinicopathological characteristics: extrahepatic disease, R2 resection, major hepatectomy, patient age, disease free interval between primary resection and diagnosis of metastases, and primary tumour characteristics [11].

The study was performed according to the REMARK guidelines[12], and approved by the institutional review boards of the Erasmus Medical Centre (MEC 2020-0294), the Institut Jules Bordet (CE2953) and Hôpital Erasme (P2019/232).

Assessment of HGPs

HGP assessment was retrospectively performed on H&E stained sections from archival tissue. The distinguishing features of the different HGPs have been described extensively in CRLM [1, 2]. The growth patterns were grouped into a dHGP, and a non-dHGP (Fig. 1).

HGPs were assessed in all available H&E slides of the resected liver metastases for each patient. All H&E sections were evaluated through light microscopy by an expert liver pathologist (MD) and at least one trained observer (AB, DH, YM). In case of doubt or disagreement about the HGP an additional observer (PV) was consulted for re-evaluation and consensus was achieved. The entire tumour-liver interface was evaluated in each available H&E slide. Each HGP was scored as a proportion of the total interface per H&E slide. Slides were not assessed if there was less than 20% of the total tumour-liver interface available, if the quality of the H&E slide was insufficient for reliable assessment or if there was no viable tumour tissue.

Average HGP proportions were subsequently calculated per metastasis and per patient. The patient-level growth pattern was determined twice for every patient using two different cut-offs.

First, patients were classified as desmoplastic if there was exclusively (100%) dHGP present at the tumour-liver interface. Patients were classified as non-desmoplastic if any amount of non-dHGP was present [1]. This cut-off is based on an observed difference in survival between these groups. A recent publication found a strong prognostic value for the presence of any non-dHGP as opposed to 100% dHGP in colorectal cancer liver metastases. These results were recently validated in an external cohort [3, 4].

Second, patients were classified following the 2017 international consensus guidelines for scoring histopathological growth patterns of liver metastases [1]. The predominant HGP, defined as the HGP found at > 50% of the tumour-liver interface, was used to classify patients into: desmoplastic, replacement and pushing. If there was no predominant HGP (no HGP present at > 50% of the tumour-liver interface), patients would be classified as mixed HGP.

Statistical analysis

Categorical data were reported as numbers and percentages, and continuous data as medians with corresponding interquartile ranges (IQR). Differences in proportions were evaluated with the Chi-Squared test. Medians between two or more groups were compared using the Mann–Whitney U test or Kruskall-Wallis test respectively. The median follow-up for survivors was calculated using reverse Kaplan–Meier method. Estimates for overall survival (OS) and recurrence free survival (RFS) were computed by Kaplan Meier analysis. OS was defined as the time from resection of liver metastases to death or loss to follow-up. RFS was defined as the time from resection of liver metastases to recurrence or death. Recurrence was defined as any tumour recurrence after liver resection, regardless of anatomic location. Survival curves for desmoplastic and non-desmoplastic patients were compared using the logrank test.

Uni- and multivariable Cox regression analyses were performed to evaluate whether HGPs were prognostic for OS and RFS. Multivariable Cox regression analysis was performed to correct for potential confounding. Covariates entered into the multivariable models were use of perioperative chemotherapy, number and largest size of liver metastases, Adam score[11], and the HGP. The results of the Cox regression were expressed as hazard ratio (HR) with corresponding 95% confidence interval (95% CI). The proportional hazards assumption was tested using Schoenfelds residuals. Missing data was addressed through pairwise deletion.

All statistical tests were two-sided. A p value lower than 0.05 was considered statistically significant. R version 4.0.2 [13]. was used for all statistical analyses.

Results

Patients characteristics

Between 2000 and 2019, 132 patients underwent curative-intent surgery for NCRNNELM in the three centres. Baseline characteristics of the population are detailed in Table 1. The cohort included liver metastases from 25 different

Table 1 Baseline characteristics per HGP (100% cut-off)

N		Total 132	Desmoplastic 26	Non-desmoplastic 106	*p*
Cohort (%)	Erasmus MC	67 (51)	18 (69)	49 (46)	**0.036**
	Brussels	65 (49)	8 (31)	57 (54)	
Sex (%)	Male	43 (33)	8 (31)	35 (33)	0.826
	Female	89 (67)	18 (69)	71 (67)	
Age (median [IQR])		57.0 [48.0, 66.0]	59.5 [50.0, 66.8]	57.0 [48.0, 66.0]	0.684
ASA (%)	ASA I	11 (10)	3 (15)	8 (9)	0.178
	ASA II	82 (72)	11 (55)	71 (76)	
	ASA III	21 (18)	6 (30)	15 (16)	
Primary tumour type (%)	Non-carcinoma	25 (19)	8 (31)	17 (16)	0.086
	Carcinoma	107 (81)	18 (69)	89 (84)	
N + Primary (%)	No	59 (59)	12 (67)	47 (57)	0.465
	Yes	41 (41)	6 (33)	35 (43)	
Nr. liver metastases (median [IQR])		1.0 [1.0, 2.0]	1.0 [1.0, 1.2]	1.0 [1.0, 2.0]	0.129
Diameter largest LM[a] (median [IQR])		33.5 [19.0, 52.2]	35.0 [20.5, 50.0]	30.0 [18.2, 54.5]	0.568
DFI (median [IQR])[b]		24.8 [9.5, 65.9]	24.3 [0.0, 107.7]	24.8 [13.7, 58.2]	0.749
Extrahepatic Metastases (%)	None	74 (72)	16 (64)	58 (74)	0.316
	Yes	29 (28)	9 (36)	20 (26)	
Chemotherapy primary tumour (%)	No	56 (44)	10 (38)	46 (46)	0.702
	Preoperative	20 (16)	6 (23)	14 (14)	
	Postoperative	27 (21)	5 (19)	22 (22)	
	Pre- and Postoperative	24 (19)	5 (19)	19 (19)	
Preoperative chemotherapy LM[a] (%)	No	60 (45)	7 (27)	53 (50)	**0.034**
	Yes	72 (55)	19 (73)	53 (50)	
Adjuvant chemotherapy LM[a] (%)	No	101 (77)	20 (77)	81 (76)	0.956
	Yes	31 (23)	6 (23)	25 (24)	
Radical resection[c] (%)	R0	110 (86)	22 (85)	88 (86)	0.828
	R1	18 (14)	4 (15)	14 (14)	
Adam score (%)	Low (0–3)	66 (50)	10 (38)	56 (53)	0.236
	Intermediate (4–6)	63 (48)	16 (62)	47 (44)	
	High (> 6)	3 (2)	0 (0)	3 (3)	

IQR Inter quartile range

[a]*LM* Liver Metastases

[b]*DFI* Disease Free Interval between treatment of the primary tumour and diagnosis of metastases

[c]Resection was considered radical if there was ≥ 1 mm between tumour and resection margin on pathological evaluation

primary tumour types (Table 2). The most common primary tumour was breast cancer (37%). The majority of the patients were operated for liver metastases from carcinoma (81%), with only a minority of patients having non-carcinoma liver metastases (19%).

HGPs could be scored in all included liver metastases. In total 501 H&E slides were evaluated (326 from the Erasmus MC cohort and 175 from the Brussels cohort). Examples are provided in Figs. 2 and 3. In the sarcoma liver metastases, a desmoplastic and a replacement-like pattern were observed (Fig. 3). This replacement-like pattern showed hepatocytes and tumour cells in close proximity, and hepatocyte replacement, without desmoplastic stroma, similar to the replacement pattern in liver metastases from epithelial origin (Fig. 3). An additional slide with hepatocyte staining is provided in supplementary Fig. 2. Because it is not known whether the interaction of mesenchymal malignant cells with hepatocytes is the same as the interaction of epithelial malignant cells with hepatocytes, this growth pattern of sarcoma liver metastases was called replacement-like.

Table 2 Origin of primary tumour for liver metastases per participating centre

N		Erasmus MC 67	Brussels 65
Primary tumor (%)	Anal cancer	3 (4)	1 (2)
	Adrenocortical carcinoma	4 (6)	0 (0)
	Cervical carcinoma	2 (3)	0 (0)
	Endometrial carcinoma	1 (1)	0 (0)
	GIST	4 (6)	6 (9)
	Leiomyosarcoma	5 (7)	2 (3)
	Liposarcoma	2 (3)	0 (0)
	Gastric carcinoma	2 (3)	0 (0)
	Melanoma	6 (9)	3 (5)
	Choroidea melanoma	5 (7)	0 (0)
	Nephroblastoma	1 (1)	0 (0)
	Renal cell carcinoma	5 (7)	1 (2)
	Non-seminoma	1 (1)	1 (2)
	Non-small cell lung cancer	1 (1)	0 (0)
	Esophageal carcinoma	3 (4)	2 (3)
	Carcinoma of the ovary	5 (7)	3 (5)
	Thyroid carcinoma	2 (3)	0 (0)
	Thymus carcinoma	1 (1)	0 (0)
	Urothelial cell carcinoma	1 (1)	0 (0)
	Pancreas carcinoma	0 (0)	3 (5)
	Small intestinal carcinoma	0 (0)	2 (3)
	Hemangiopericytoma	0 (0)	1 (2)
	ORL[a] carcinoma	0 (0)	3 (5)
	Vaters ampulla carcinoma	0 (0)	1 (2)
	Breast carcinoma	13 (19)	36 (55)

[a]*ORL* Otorinolaryngology

Histopathological growth patterns

The patient characteristics stratified by HGP according to the 100% desmoplastic cut-off are presented in Table 1. A desmoplastic pattern was observed in 26 (20%) patients and comprised 27% (18/67) of the Erasmus MC cohort and 12% (8/65) of the Bordet-Erasme cohort ($p = 0.036$). There were no significant differences in 5-year OS or RFS between the Erasmus MC and Bordet-Erasme cohort (39% vs 47% $p = 0.229$ and 17 vs 21% $p = 0.916$). The distribution of HGPs on a per patient level is graphically presented in Fig. 4. Preoperative chemotherapy was given to 73% (19/26) of the desmoplastic group compared to 50% (53/106) of the non-desmoplastic group ($p = 0.034$). Adjuvant chemotherapy was given to 23% (6/26) of the desmoplastic group compared to 24% (25/106) of the non-desmoplastic group ($p = 0.956$). There were no differences in Adam score between the desmoplastic and the non-desmoplastic group ($p = 0.236$). For the breast cancer liver metastases there was no significant association between HGP and estrogen, progesterone or her2 receptor status (supplementary Table 1a.)

Survival

Follow-up data for OS were available in 129 patients. Follow-up data for RFS were available in 124 patients. Median follow-up for survivors was 74 months for all patients (35–151 months IQR). The Erasmus MC cohort had a significantly longer median follow-up of 106 months (57–151 IQR) compared to the Bordet-Erasme cohort (56 months, 27–151 IQR)(p 0.03).

The OS was significantly longer in desmoplastic versus non-desmoplastic metastases logrank $p = 0.031$ (Fig. 5), reaching an estimated 5-year OS of 53% (36–78%, 95% CI), and 40% (30–53%, 95%CI), respectively. Median OS was 70 months (48 months – Not Reached 95% CI) and 44 months (35–70 months 95% CI) respectively. Similarly, RFS was significantly longer in desmoplastic versus with non-desmoplastic patients (logrank $p = 0.004$, Fig. 5), reaching a 5-year RFS of 33% (19–61% 95% CI) and 15% (9–27% 95% CI), respectively. Median RFS was 33 months (16 months – Not Reached 95% CI) and 14 months (9–19 months 95% CI) respectively.

The univariable and multivariable cox regression analyses for OS and RFS are shown in Table 3. Multivariable analysis showed a significant association between HGP and survival outcomes with favourable results in desmoplastic NCRNNELM, both for OS (Adjusted HR 0.51, $p = 0.04$) and for RFS (adjusted HR 0.38, $p < 0.01$). Adam score was also predictive for OS and RFS (Table 3).

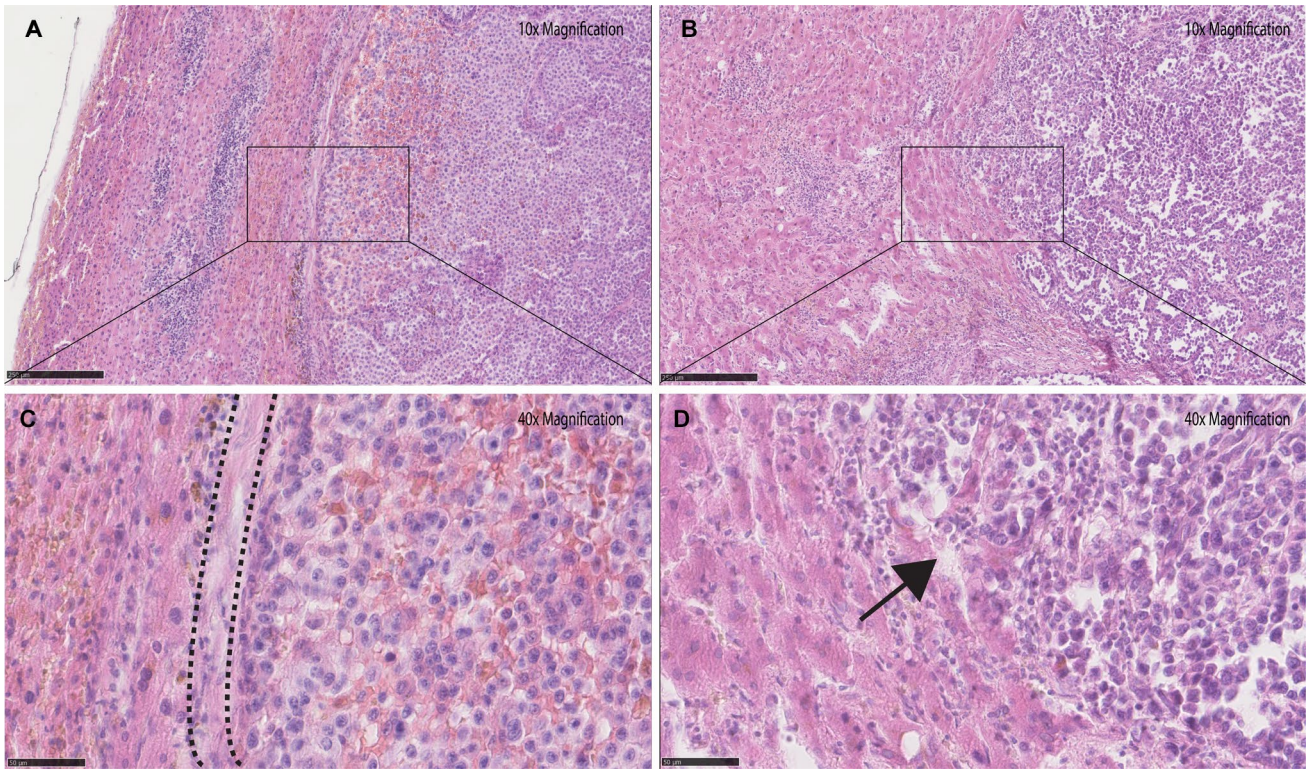

Fig. 2 Histopathological growth patterns in melanoma liver metastases. **A** Desmoplastic (10 × magnificantion) **B** Replacement (10 × magnification) **C** Desmoplastic (40 × magnification), dotted lines annotate the fibrotic rim **D** Replacement(40 × magnification) Scale bar represents 250 um for 10 × and 50 um for 40 × magnification. Arrow highlights hepatocytes surrounded by tumour cells not separated by desmoplastic stroma

HGP and survival analysis (2017 Consensus, using predominant HGP)

Out of the 132 patients, 74 (56%) had a predominantly desmoplastic HGP, 57 (43%) had a predominantly replacement HGP and 1 (1%) had a predominantly pushing HGP. No patients had a mixed HGP. When classified according to the consensus guidelines, no statistically significant differences between the HGPs with regards to median number of metastases ($p = 0.157$), median diameter of the largest metastasis ($p = 0.852$), use of perioperative chemotherapy ($p = 0.128$) and Adam score ($p = 0.185$) were observed. For the breast cancer liver metastases there was no significant association between HGP and estrogen, progesterone or her2 receptor status (supplementary Table 1b.) The baseline characteristics per predominant HGP are presented in supplementary Table 2.

Due to the single incidence of predominant pushing HGP the survival analyses were limited to a comparison between predominant desmoplastic and predominant replacement HGP. The estimated 5-year overall survival was 46% in desmoplastic patients (35–61%, 95% CI) and 37% in replacement patients (25–56%, 95%CI). The median OS was 58 months (44–85 months 95% CI) and 41 months (25–110 months 95% CI), respectively. Log-rank test showed a statistically significant difference in OS between both groups (p 0.032) in favour of desmoplastic patients (Supplementary Fig. 6).

The estimated 5-year RFS was 27% in the desmoplastic patients (17–42% 95% CI) compared to 9% in the replacement patients (3–24% 95%CI). The median RFS was 21 months (14–36 months 95% CI) and 11 months (7–19 months 95% CI), respectively. Log rank test showed a statistically significant difference in RFS in favour of desmoplastic patients ($p = 0.001$, Supplementary Fig. 6).

The univariable and multivariable cox regression analyses for OS and RFS are shown in supplementary Table 2. Multivariable analysis showed a significant association between HGP and postoperative outcomes with favourable results in desmoplastic NCRNNELM for RFS (Adjusted HR 0.42, $p < 0.01$). Adjusted HR for OS was 0.62, $p < 0.06$. Besides HGP, Adam score was also predictive for OS and RFS (Supplementary Table 3).

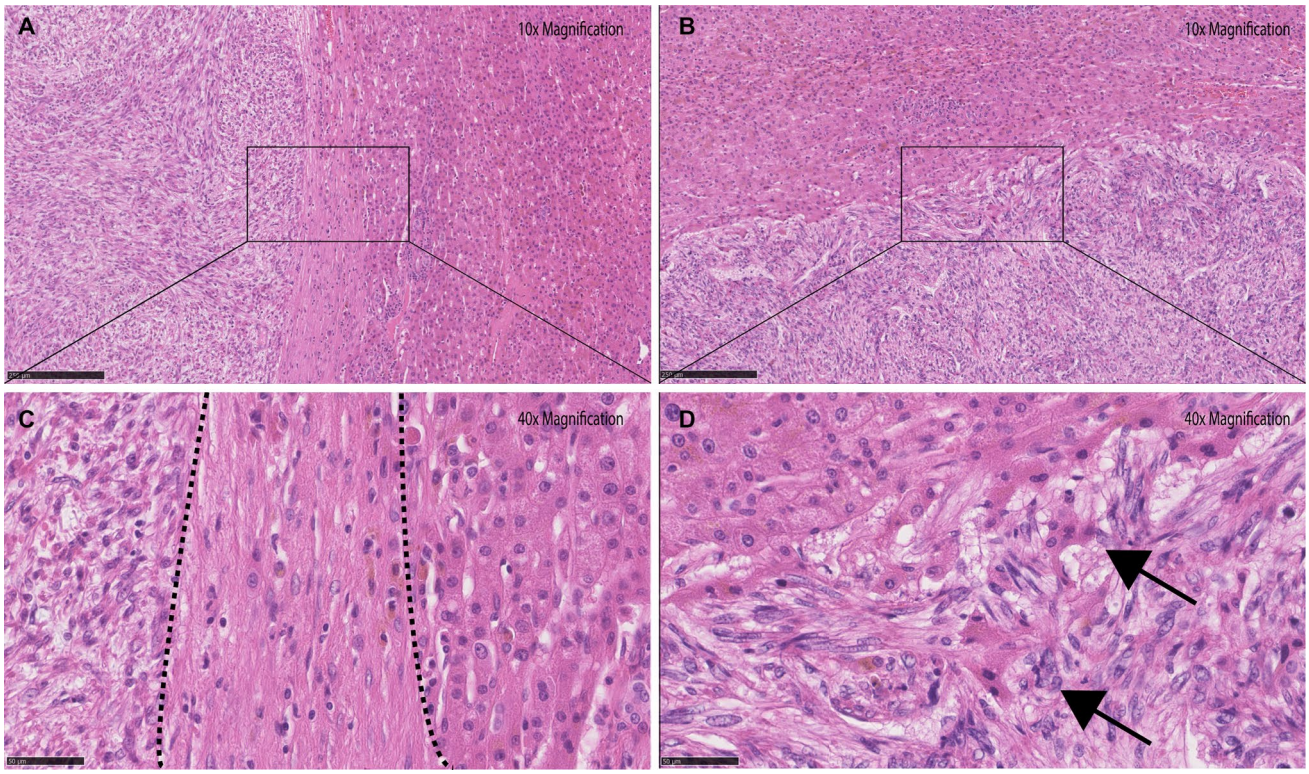

Fig. 3 Histopathological growth patterns in leiomyosarcoma liver metastases. **A** Desmoplastic (10×magnificantion) **B** Replacement (10×magnification) **C** Desmoplastic (40×magnification), dotted lines annotate the fibrotic rim **D** Replacement(40×magnification) Scale bar represents 250 um for 10×and 50 um for 40×magnification. Arrow highlights hepatocytes surrounded by tumour cells not separated by desmoplastic stroma

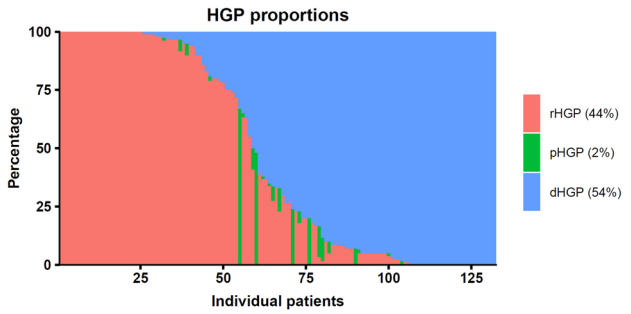

Fig. 4 Proportions of HGPs on patient level; Each vertical bar represents a single patient. *rHGP* Replacement Growth Pattern, *pHGP* Pushing Growth Pattern, *dHGP* Desmoplastic Growth pattern

Discussion

In the current study, we observed that HGPs can be documented in liver metastases from a variety of primary tumours, including those originating outside of the gastro-intestinal tract. Despite the considerable heterogeneity of this series, desmoplastic, replacement and pushing histological features could be identified in all the evaluated metastases.

In the non-epithelial liver metastases a desmoplastic and a replacement-like growth pattern were observed. To our knowledge, HGPs have only been described in primary and secondary liver tumours of epithelial origin [1, 14–16]. Sarcomas are non-epithelial tumours, thus the growth patterns observed in this study may merely resemble the HGPs that have been observed in epithelial tumours from a morphological and not necessarily from a biological point of view. Further study in a larger, less heterogeneous sample is needed to evaluate whether liver metastases from non-epithelial tumours exhibit the same HGPs as metastases from epithelial tumours.

HGPs of epithelial tumours have been documented in previous studies for a limited number of primary and secondary liver tumours. A similar correlation between desmoplastic HGP and favourable prognosis was reported in melanoma, breast, and pancreatic cancer patients with liver metastases, as well as in patients with hepatocellular carcinoma [2, 5, 14–16].

Desmoplastic HGP was more common in the Erasmus MC cohort, compared to the Brussels cohort in this study. This may have been influenced by different local practices

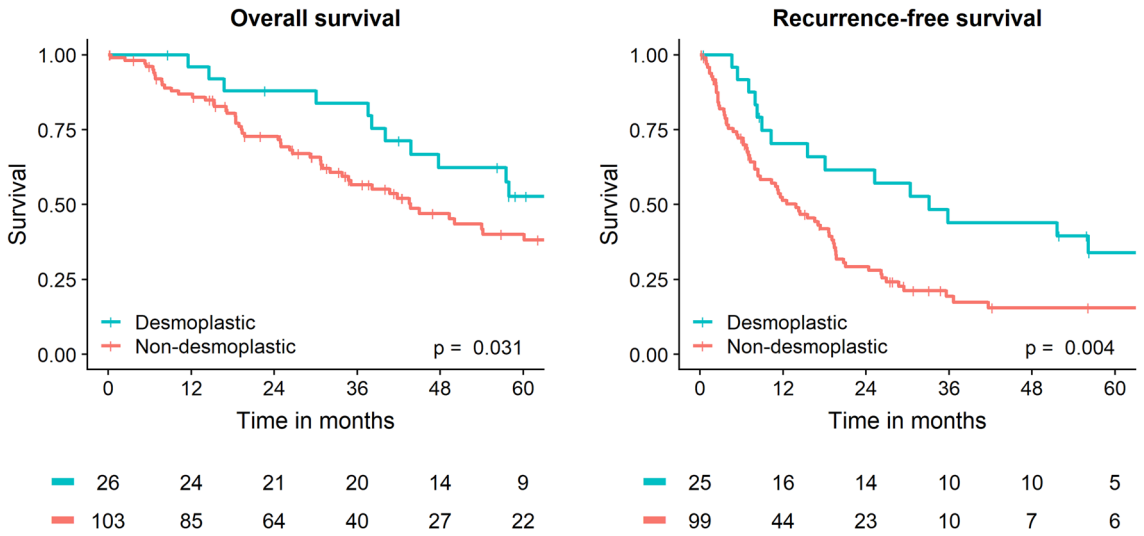

Fig. 5 Kaplan Meier Curves for Overall and Recurrence free survival per HGP (100% Cut-off)

Table 3 Uni-and multivariable cox regression for OS and RFS (100% cut-off)

Overall survival	Univariate	*p*	MV (*n* = 123)	*P*
Perioperative chemotherapy	1.03 [0.65–1.65]	0.9	1.07 [0.64–1.78]	0.79
Diameter largest metastasis (cm)	1.44 [0.89–2.31]	0.14	1.39 [0.84–2.31]	0.2
Nr. liver metastases (multiple)	1.03 [0.95–1.12]	0.48	1.03 [0.94–1.12]	0.54
Adam score	1.15 [0.98–1.35]	0.09	1.17 [0.99–1.37]	0.06
HGP (Non-desmoplastic)	0.52 [0.28–0.95]	0.03	0.49 [0.25–0.93]	0.03
Recurrence free survival	Univariate	*p*	MV (*n* = 118)	*P*
Perioperative chemotherapy	0.89 [0.58–1.36]	0.59	0.91 [0.58–1.44]	0.7
Diameter largest metastasis (cm)	1.34 [0.87–2.09]	0.19	1.32 [0.83–2.11]	0.24
Nr. liver metastases (multiple)	1.02 [0.93–1.12]	0.63	1.01 [0.93–1.11]	0.75
Adam score	1.15 [0.99–1.35]	0.07	1.21 [1.03–1.42]	0.02
HGP (Non-desmoplastic)	0.44 [0.25–0.78]	<0.01	0.37 [0.20–0.70]	<0.01

OS Overall survival, *RFS* Recurrence free survival, *HGP* Histopathological growth pattern

with regards to preoperative chemotherapy, which was much more frequently administered in the Brussels cohort (74%) compared to the Erasmus MC cohort (36%). Preoperative chemotherapy has been described to alter the histopathological growth patterns in CRLM [17]. Another contributing factor may be the composition of the cohort. Previous studies have found different proportions of HGPs in liver metastases depending on the origin of the primary tumour [14, 15]. The Brussels cohort consists of 55% breast cancer liver metastases (Table 2), which have been shown to exhibit more replacement HGP compared to CRLM [14]. If the origin of the primary tumour influences the proportion of HGPs present, differences in the composition of the cohort may affect the proportions of observed HGPs. It seems unlikely that intra-observer variablility played a large role to explain this difference. HGPs have been demonstrated to be a reliable and replicable biomarker in CRLM [18], all assessments in the current study were performed by pathologists (MD, PV) with experience in scoring HGPs and the same pathologist (PV) was consulted for both cohorts.

Additionally, we found that HGPs of NCRNNELM are associated with the prognosis in patients undergoing resection. Relying on a 100% cut-off (i.e. pure desmoplastic versus any non-desmoplastic component) that has been recently validated in CRLM [3], we found that dHGP was a significant predictor for favourable OS on log rank test and in multivariable regression analysis when correcting for confounders. Pure desmoplastic HGP was also associated with a significantly longer RFS on both uni- and multivariable Cox regression. A similar association was found for OS

and RFS when using the predominant HGP, with marginally lower effect estimates. Given the small number of patients, the ideal HGP cut-off point for liver metastases from non-colorectal and non-neuroendocrine origin remains unknown. However, the categorization into pure desmoplastic and non-pure desmoplastic HGPs has a strong advantage for clinical use due to its easiness and reproducibility compared to the measurement of the respective percentages of different HGPs at the tumour-liver interface [3]. In this study only one patient had a predominant pushing HGP, making it impossible to assess the prognostic importance of a predominant pushing HGP in patients with NCRNNELM.

Taken together, the observation of similar histological phenotypes associated with similar prognostic tendencies between NCRNNELM and CRLM might suggest a common underlying biology. DHGP has previously been linked to an enrichment of immune cells in the tumour microenvironment. Desmoplastic HGP in CRLM displays an increase in CD8 + T cells in the tumour microenvironment, compared to non-desmoplastic CRLM [19]. In addition, the desmoplastic phenotype has been associated with MSI tumours [4]. MSI tumours have a genetic hypermutability that leads to the expression of mutational neoantigens and potential immunogenicity [20, 21]. This could suggest that the desmoplastic phenotype is an expression of increased anti-cancer immunity [4]. Evaluation of the presence of these characteristics in NCRNNELM could provide more evidence towards common underlying mechanisms, related to host responses and anti-tumour immunity in the development of HGPs.

Furthermore, in the specific context of NCRNNELM, the better understanding of the mechanisms leading to different HGPs and their prediction with non-invasive methods could represent a benefit for therapeutic decision-making [22]. Currently, surgical decision remains poorly individualized in these cases, with a limited value from different risk factors and models [23]. In particular, and similarly to ongoing works in CRLM, the preoperative definition of HGPs of NCRNNELM with new imaging tools [22], could contribute to personalized decision making, using HGP as a surrogate for metastatic behaviour.

The reliability and replicability of HGPs as a biomarker has been previously demonstrated in colorectal cancer liver metastases [24]. In addition, the intra tumour heterogeneity was low, which means that a limited number of H&E slides is necessary for accurate HGP determination [24]. High accuracy combined with ease of use make HGPs a strong candidate biomarker for patients with NCRNNELM.

This study is limited by its sample size. Intentionally curative resection for liver metastases from NCRNNELM remains uncommon in clinical practice, making it difficult to gather many cases. The small sample size combined with a large tumour heterogeneity means that any results should be interpreted with caution. The included tumours have different prognoses with regards to OS and RFS. Due to the small sample size, it was also not possible to correlate primary tumour type to type of HGPs or survival. In addition, the use of preoperative chemotherapy varies per tumour type, which may affect the reliability of assessment of the HGP [17]. In this study, the patients with desmoplastic HGP had undergone preoperative chemotherapy more frequently, compared to patients with non-desmoplastic HGP. This is in line with previous studies that describe that desmoplastic HGP is more common after preoperative chemotherapy. It is not clear whether the increased prevalence of desmoplastic HGP is due to a biological change induced by preoperative chemotherapy or due to an inherent limitation of the current assessment of HGPs [17]. The impact of HGPs on clinical prognosis in this group should therefore be interpreted with care. As discussed before, the evaluation of the presence of HGPs in sarcoma liver metastases requires special consideration.

To our knowledge, this is the only cohort describing HGPs in NCRNNELM, serving as a proof of concept that similar phenotypes than those reported in CRLM could be identified in these cases. In addition, as in CRLM, these HGPs appear of significant prognostic value. Together with previous works in CRLM [25–27] and in other secondary liver tumours [14, 15, 28], this strongly suggests that the micro-organization of liver metastases could represent a pan-cancer biomarker of metastatic behaviour, resulting from interactions between cancer cells and liver microenvironment, relying on biological/molecular drivers, eventually only marginally influenced by the primary tumour type. Further investigations into features associated with the HGPs like vessel co-option and immune microenvironment, are necessary to support this hypothesis.

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Data availability Data will be available on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose. No funding was received for conducting this study.

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