

MATTERS ARISING OPEN



What's in a name? Refining the nomenclature of liver metastases growth patterns by changing “desmoplastic” to “encapsulated”

Carlos Fernández Moro^{1,2,3,7}, Béla Bozóky^{2,7}, Natalie Geyer¹, Jennie Engstrand⁴, Luc Dirix⁵, Peter Vermeulen⁵✉ and Marco Gerling^{1,6}✉

© The Author(s) 2023

ARISING FROM E. Latacz et al. *Br J Cancer* <https://doi.org/10.1038/s41416-022-01859-7> (2022)

BJC Reports; <https://doi.org/10.1038/s44276-023-00018-6>

Liver metastases growth patterns are conventionally classified as either “replacement” or “desmoplastic”. We and others have suggested this classification in the latest international consensus guidelines recently published in the *British Journal of Cancer* [1]. While other rare patterns exist, “replacement” and “desmoplastic” are the most common patterns. They are associated with clear differences in survival, such that predominantly desmoplastic colorectal cancer metastases have a more favorable liver relapse-free and overall survival, as demonstrated in large international, retrospective studies [1, 2].

The growth patterns are currently not a part of the routine assessment of liver metastases in most pathology departments. Because they outperform other known prognostic markers [1], we hope and actively work for them to be implemented in routine diagnostics. Given their potential clinical implementation, it will be important to carefully reassess the growth patterns’ nomenclature to avoid misunderstandings. Against this background, we appreciate the suggestion by Kong and colleagues to change the term “replacement” to “infiltrative” [3]. Nevertheless, we argue for keeping the current term, “replacement” because during infiltration into the liver, cancer cells morphologically indeed co-opt the sinusoidal blood vessels by taking the place of the hepatocytes as outlined previously [4].

However, we here suggest changing the term for “desmoplastic” to “encapsulated”, based on the careful reassessment of the connotations of both terms and in light of new experimental data. The name change serves two purposes: 1. It avoids confusion with a common connotation of “desmoplasia,” which refers to stromal activation, associated with aggressive tumor invasion; 2. It takes into account new experimental evidence that links the formation of the perimetastatic capsule to a benign-like fibrotic reaction as part of a reparative hepatic process.

Firstly, “encapsulated” avoids conflation with the so-called “desmoplastic” stroma, which has more commonly been associated with aggressive tumor growth, most prominently in pancreatic ductal adenocarcinoma [5], but also in other

malignancies, such as primary colorectal cancer [6]. Although the term “desmoplasia” is loosely defined in the literature and may refer to any pathological stroma regardless of the mechanism, many physicians and researchers may perceive and interpret ‘desmoplasia’ as the result of active, aggressive tumor growth; this prevailing view is supported by studies that have shown negative correlations between the amount of desmoplasia and tumor-related outcomes [5, 6]. The connection of negative outcomes with “desmoplasia” is at odds with the fibrotic capsule seen in patients with liver metastases, because the stromal rim in liver metastases is associated with a significant survival advantage [1]. We acknowledge that the protective effects of the desmoplastic intratumoral stroma are being increasingly recognized. Nevertheless, because we and others in the field aim at the clinical implementation of the growth patterns, we argue for a terminology that avoids the possibility of confounding the perimetastatic rim with intratumoral desmoplasia, which would be achieved by using “encapsulated” instead.

Recent functional evidence from our group has shed light on the processes underlying capsule formation [7]. We have analyzed human colorectal cancer liver metastases and found remnants of liver parenchyma predominantly in the outer zone of the rim. Protein profiling revealed a zonation of the rim, such that benign-like stroma markers were seen in the outer part of the rim. In contrast, the tumor-adjacent inner rim showed similarities to the stroma of the metastasis centrum. We also observed a strong positive correlation between neoadjuvant chemotherapy and the presence of the capsule, which had been described before in prospectively collected specimens from a randomized clinical trial [8]. Together, these data suggest that reduced tumor cell fitness, for example, as a consequence of chemotherapy, is associated with capsule formation and that the resulting capsule represents a reparative hepatic process rather than tumor-induced “desmoplasia” in its narrower sense. We next treated mice with chemotherapy and used a genetic model to ablate established murine liver metastases. We consistently observed perimetastatic capsule

¹Department of Biosciences and Nutrition, Karolinska Institutet, 14183 Huddinge, Sweden. ²Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm 14186, Sweden. ³Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, 14186 Stockholm, Sweden. ⁴Department of Clinical Science, Intervention and Technology, Division of Surgery, Karolinska Institutet, Karolinska University Hospital, 14152 Stockholm, Sweden. ⁵Translational Cancer Research Unit (GZA Hospitals and University of Antwerp), Antwerp, Belgium. ⁶Theme Cancer, Karolinska University Hospital, 17 176 Solna, Sweden. ⁷These authors contributed equally: Carlos Fernández Moro, Béla Bozóky. ✉email: peter.vermeulen@gza.be; marco.gerling@ki.se

formation, linking reduced tumor cell fitness to the formation of encapsulating fibrosis. Similarly, in a previous study, replacement could be converted to encapsulated growth when reducing cancer cell fitness by interfering with cell motility in a murine colorectal cancer liver metastasis model [9].

The term “encapsulated” has been used before in some studies to denote a growth pattern corresponding to the “desmoplastic” pattern as described in the current scoring guidelines [1, 10]. Based on the reasoning above, we suggest using “encapsulated” instead of “desmoplastic” in future works that address the growth patterns, and for clinical scoring algorithms.

REFERENCES

- Latacz E, Höppener D, Bohlok A, Leduc S, Tabariès S, Fernández Moro C, et al. Histopathological growth patterns of liver metastasis: updated consensus guidelines for pattern scoring, perspectives and recent mechanistic insights. *Br J Cancer*. 2022. <https://doi.org/10.1038/s41416-022-01859-7>.
- Höppener DJ, Galjart B, Nierop PMH, Buisman FE, van der Stok EP, Coebergh van den Braak RRJ, et al. Histopathological growth patterns and survival after resection of colorectal liver metastasis: an external validation study. *JNCI Cancer Spectrum*. 2021. <https://doi.org/10.1093/jncics/pkab026>.
- Kong B, Zhang Q, Zhang G. Use the term ‘infiltrative’ instead of ‘replacement’ when defining histopathological growth pattern in patients with liver cancer. *Br J Cancer*. 2023;128:489–90. <https://doi.org/10.1038/s41416-022-02121-w>
- Vermeulen PB, Latacz E, Van den Hauwe M, Van den Hauwe M, Dirix L. Comment on ‘Use the term “infiltrative” instead of “replacement” when defining histopathological growth pattern in patients with liver cancer’ by Kong B et al. *Br J Cancer*. 2023;128. <https://doi.org/10.1038/s41416-023-02173-6>.
- Whatcott CJ, Diep CH, Jiang P, Watanabe A, LoBello J, Sima C, et al. Desmoplasia in primary tumors and metastatic lesions of pancreatic cancer. *Clin Cancer Res*. 2015;21:3561–8. <https://doi.org/10.1158/1078-0432.CCR-14-1051>.
- Ueno H, Kanemitsu Y, Sekine S, Ishiguro M, Ito E, Hashiguchi Y, et al. Desmoplastic pattern at the tumor front defines poor-prognosis subtypes of colorectal cancer. *Am J Surg Pathol*. 2017;41:1506–12. <https://doi.org/10.1097/PAS.0000000000000946>
- Fernández Moro C, Geyer N, Harrizi S, Hamidi Y, Söderqvist S, Kuznyecov D, et al. An idiosyncratic zoned stroma encapsulates desmoplastic liver metastases and originates from injured liver. *Nat Commun*. 2023;14:5024. <https://doi.org/10.1038/s41467-023-40688-x>.
- Nierop PM, Höppener DJ, Buisman FE, van der Stok EP, Galjart B, Balachandran VP, et al. Preoperative systemic chemotherapy alters the histopathological growth patterns of colorectal liver metastases. *J Pathol Clin Res*. 2022;8:48–64. <https://doi.org/10.1002/cjp2.235>.
- Frentzas S, Simoneau E, Bridgeman VL, Vermeulen PB, Foo S, Kostaras E, et al. Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. *Nat Med*. 2016;22:1294–302. <https://doi.org/10.1038/nm.4197>.
- Fernández Moro C, Bozóky B, Gerling M. Growth patterns of colorectal cancer liver metastases and their impact on prognosis: a systematic review. *BMJ Open Gastroenterol*. 2018;5:e000217. <https://doi.org/10.1136/bmjgast-2018-000217>.

AUTHOR CONTRIBUTIONS

MG, PV, and CFM wrote the manuscript. BB, LD, NG, and JE commented on the manuscript. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Peter Vermeulen or Marco Gerling.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2023